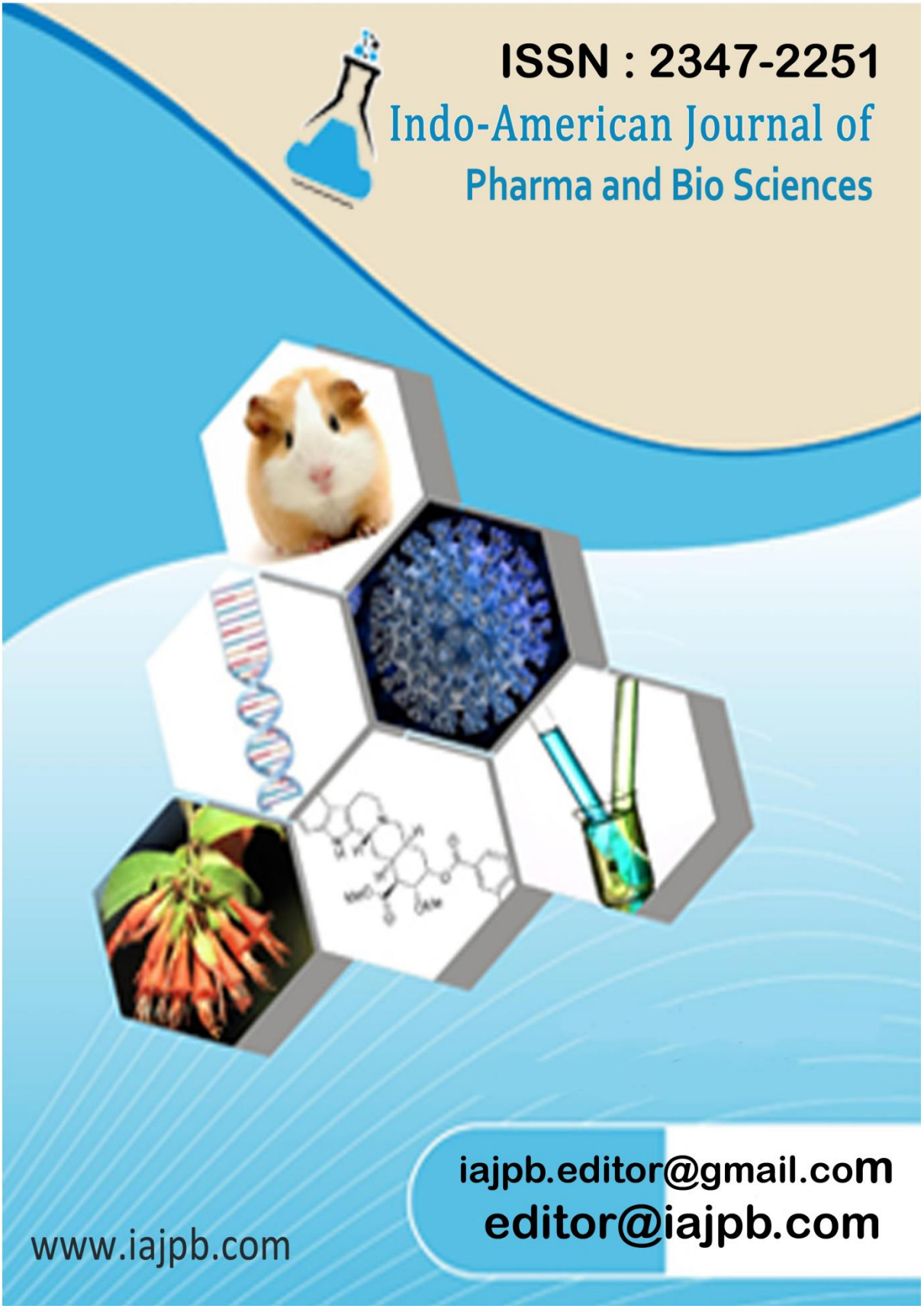
Indo-American Journal of Pharma and Bio Sciences

ISSN 2347-2251 www.iajpb.com
Vol. 22, Issue 1, Jan 2024



Indo-American Journal of Pharma and Bio Sciences

ISSN 2347-2251 www.iajpb.com
Vol. 22, Issue 1, Jan 2024

Targeting S100A8/S100A9: A Proteomic Approach to Uncover Therapeutic Avenues in Aortic Dissection

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ABSTRACT

SIRT1 is a histone deacetylase that is highly conserved and relies on nicotinamide adenine dinucleotide (NAD+). Numerous pathologic processes, such as cell division, survival, proliferation, autophagy, and oxidative stress, are regulated by it. The heart and cardiomyocytes are shielded against pathology-related stress by therapeutic SIRT1 activation, especially myocardial ischemia/reperfusion (I/R). One crucial metabolic mechanism that helps people survive energy or nutritional shortages, hypoxia, or oxidative stress is autophagy. Autophagy has two sides when it comes to myocardial injury. While excessive autophagy after reperfusion depletes the cellular components and causes autophagic cell death, autophagy activation during the ischemia phase eliminates excess metabolic waste and helps preserve cardiac myocyte survival. Growing studies on I/R have shown that SIRT1 controls myocardial I/R and is implicated in the process of autophagy. SIRT1 controls autophagy by a number of mechanisms, including the deacetylation of LC3, ATGs, and FOXOs. According to recent research, SIRT1-mediated autophagy has distinct functions depending on the degree of myocardial I/R damage. Targeting the mechanism of SIRT1-mediated autophagy at various phases of I/Rinjury may lead to the development of novel small-molecule medicines, miRNA activators, or blockers. For instance, coptisine, curcumin, berberine, and some miRNAs during reperfusion were implicated in controlling the SIRT1-autophagyaxis, exerting a cardioprotective impact, whereas resveratrol, sevoflurane, quercetin, and melatonin were involved in the ischemic stage. To determine treatment approaches for myocardial I/R damage, we discuss here the potential pathways of autophagy regulation by SIRT1 in myocardial I/R injury and the associated molecular pharmacological applications.

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1. Introduction

According to the American Heart Association, about one in forty persons may have a heart attack, making coronary artery disease a condition with a high morbidity and death rate globally [1]. An examination of 23 published studies that followed 14,211 individuals prospectively after myocardial infarction (MI) revealed that on average After their first MI, 23% of patients passed away before they arrived at the hospital, and another 13% passed away while they were being admitted [2]. A common therapeutic approach that reduces myocardial ischemia damage and reduces infarct size is prompt myocardial reperfusion using percutaneous coronary intervention; nevertheless, perfusion therapy exacerbates cell death and further leads to Abbreviations: FOXO1, forkhead box transcription factor O1; Nrf2, nuclear factor E2-related factor 2; I/R, ischemia/reperfusion; TNF-α, tumor necrosis factorα; IL-1β, interleukin-1β; IL-6, interleukin-6; AKT, protein kinase B; SODs, superoxided dismutases; GSH, glutathione; NF-κB, nuclear factor kappa-B, PDH, pyruvate dehydrogenase; NOD, nucleotide oligomerization domain; H/R, hypoxia/reoxygenation; Bcl-2, B-cell lymphoma-2; Bcl-xL, BCL-likeX; Bax,BCL-2-associatedXprotein;

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AMPK,AMP-activated proteinkinase; mTORC1,rapamycin; BNIP3, adenovirus E1B 19 kDa-interacting protein 3; LC3, light chain 3; Rab7, brain 7; EP300, E1A binding protein p300; PE, phosphatidylethanolamine; DOR, reactive oxygen species; PINK1, PTEN-induced kinase 1; Parkin, E3 ubiquitin-protein ligase; MDA, malondialdehyde; TMBIM6, transmembrane Bax inactivator 1 motif-containing 6; Mst1, macrophage stimulating 1; MRTF-A, myocardin-related transcription factor A; HDAC3, Histone deacetylase 3; Bmal1, brain and muscle Arnt-like protein 1. damage caused by myocardial ischemia-reperfusion (I/R) [3,4]. The 8-year mortality rate for elderly individuals with myocardial infarction treated with reperfusion treatment is still 49% [5]. Many medications have been developed to treat myocardial I/R, including as aspirin, cyclosporine A, and exenatide. Despite their potential to improve prognosis, the majority of these medications still have a number of drawbacks, including ineffective targeting and serious adverse effects. These restrictions have inspired researchers to create more potent medications and cutting-edge treatment approaches. [6]. Sirtuins are a conserved family of deacetylases that are reliant on nicotinamide adenine dinucleotide (NAD+) and adenosine diphosphate (ADP) ribosyltransferases (ARTs). NAD+-consuming enzymes include both NAD+-dependent deacetylases and ADP ribosyltransferases [7]. The ART family may preserve transcriptional control, energy metabolism, cell death, and genomic integrity by catalyzing the ADP-ribosylation of amino acids, nucleotides, and antibiotics as well as the dephosphorylation of tRNA splicing intermediates [8]. Originally identified as class III histone deacetylases, the sirtuins family is distinguished from other deacetylases by a unique NAD+-dependent mechanism [9]. In order to convert NAD+ to otinamide and O-ace-tyl-ADP ribose, which in turn eliminates the acetyl group from the target substrate, deacetylation of sirtuins necessitates NAD+ and its metabolites as substrates and cofactors, hence coordinating biological processes including genome stability and epigenetic state [10]. SIRT1–SIRT7, members of the sirtuin family, are distributed differentially inside cells. SIRT1 and SIRT2 are found in the cytoplasm and the nucleus, whereas SIRT3 and SIRT4 are found in the mitochondria and SIRT6 and SIRT7 are found in the nucleus. SIRT1 contains the most DNA and amino acid sequences overall among them [11,12]. Sirtuins also differ in their renzymatic activities. SIRT1 is involved in the regulation of several cellular processes, such as cell proliferation, differentiation, autophagy, and cell survival, and primarily carries out its biological activity by deacetylating different histone and non-histone proteins [13]. By deacetylating p53, SIRT1 suppresses its transcriptional activity, hence promoting cell survival and proliferation [14]. Forkhead box O3 (FOXO3) deacetylation by SIRT1 improves FOXO3-induced cell cycle arrest. Apoptosis mediated by FOXO3 [15]. By increasing autophagy levels via Beclin1 deacetylation at K430 and K437, SIRT1 lessens renal cell damage during sepsis [16]. While SIRT1-deficient animals show developmental abnormalities in a range of tissue types, including retinal, septal, and valvular heart defects [18,19], embryonic mice show high levels of SIRT1 [17], indicating a crucial function for SIRT1 in differentiating. Along with the aforementioned regulatory functions, SIRT1 is a longevity factor that may prolong the lifetime of several species via calorie restriction processes. According to a well-known theory called the "excitatory" hypothesis, caloric restriction as a longevity strategy might give biological stress resistance, and the accumulation of such traits can shield the heart from I/R damage [20,21]. Evidence suggests that SIRT1 may promote mitochondrial function and reduce stress signaling via calorie restriction, hence improving functional recovery after total cardiac ischemia [22]. The possible mechanism of SIRT1's beneficial involvement in myocardial I/R damage is yet unknown, however. SIRT1 is thought to be strongly associated with the control of autophagy in a number of illnesses, particularly in myocardial I/R, according to further research on autophagy [21]. Following the first window of ischemia preconditioning, the hearts of SIRT1-overexpressing animals showed decreased cytoplasmic acetylation and enhanced autophagy, as well as endogenous protection against I/R damage [23]. Therefore, by controlling autophagy during myocardial I/R injury, SIRT1 shields the heart from more harm. Nevertheless, the precise processes and therapeutic uses by which SIRT1 controls autophagy remain unclear. Therefore, we provide an overview of the current clinical drug application methodologies to identify novel therapeutic targets for myocardial I/R damage as well as the potential pathways by which SIRT1 controls

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autophagy in this condition (Fig. 1). 2. Injury to myocardial ischemia-reperfusion

Myocardial ischemia, which is often caused by partial or total blockage of the coronary artery, is a decrease in blood flow to the heart that makes it impossible for the heart muscle to obtain enough oxygen. When myocardial ischemia is severe and persistent, it may induce myocardial infarction, an irreversible lesion that is one of the main causes of mortality globally [24, 25]. Revascularization is the process by which the heart's shape and function are restored by reperfusion after ischemia. In addition to saving the ischemic myocardium, reperfusion causes more damage during this phase, which is different from the ischemic phase in terms of the mechanism. Therefore, it is crucial to discover specific treatment techniques aiming at avoiding or minimizing myocardial damage caused by I/R.

The main cause of myocardial damage during the ischemia stage is ion pump system failure, which is followed by calcium buildup and acidosis. Anaerobic metabolism generates a significant quantity of H+ due to oxygen deprivation, which activates the H+-Na+ exchange system and causes further Na+ input into cells, worsening Ca2+ buildup [26]. This is followed by cellular acidosis, an increase in anaerobic glycolysis, a disruption of protein synthesis and lipid transport, lysosomal membrane rupture, DNA strand breakage, and nuclear chromatin agglutination. Furthermore, ischemia and hypoxia may cause a rise in reactive oxygen species, which might result in lipid

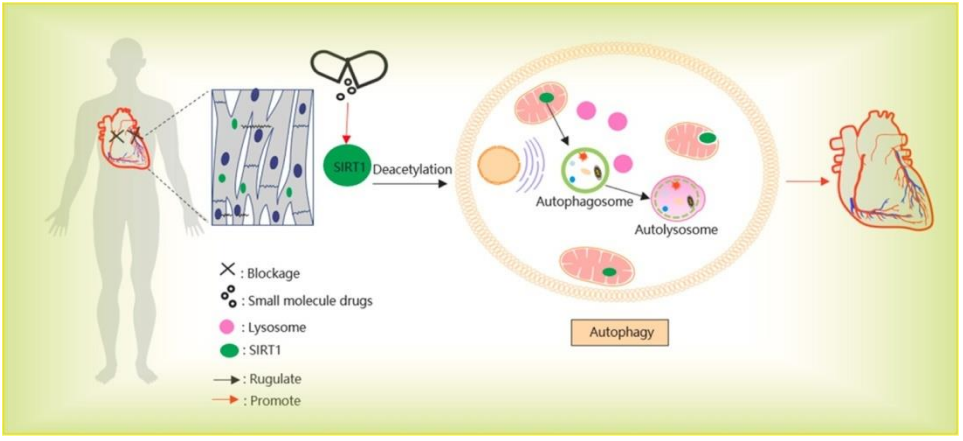

Fig.1. Mechanism ofSIRT1 in myocardialischemia/reperfusion.

Small-molecule medications may alleviate cardiac ischemia-reperfusion damage by targeting SIRT1 in the mitochondria and controlling autophagy by deacetylating it. cell death, cytoskeletal damage, and disintegration [27].

As oxygen is restored after reperfusion, oxidative phosphorylation starts up again, giving collagen fibers energy. Nevertheless, prolonged contraction and subsequent spasm of these fibers due to an excessive buildup of Ca2+ during the ischemia phase harms cardiomyocytes [28, 29]. Consequently, the heart is shielded from reperfusion harm by a brief systolic block at the start of reperfusion. Additionally, the cells experience edema during coronary reperfusion when the extracellular osmotic pressure quickly returns to normal, which causes the myocardium to mechanically stretch [30]. As a result, the muscular membranes' integrity can be jeopardized. Moreover, peroxidation of the remaining tissue brought on by reperfusion after ischemia might harm organelles, proteins, DNA, and cellular membranes. Additional oxygen radicals may be released as a result of damaged cell membranes, which may then indirectly encourage cardiomyocyte apoptosis via redox processes, ultimately resulting in myocyte death and serious heart damage. Therefore, when blood oxygen levels have been restored, peroxidation and muscular spasms are often linked to injuries sustained during the perfusion period. Notably, the inflammatory response during I/Risa is a complicated system with many different parts and how they interact. Reactive oxygen species (ROS) produced in large quantities by organelles like mitochondria are essential for starting and sustaining the inflammatory phase of I/R injury. Both cardiac resident cells and circulating leukocytes, on the other hand, support the inflammatory response. They easily penetrate mesenchymal tissues through ischemic-damaged vascular endothelium and exacerbate the parenchymal and car-diomyocyte cell death programs through necrotic, apoptotic, and autophagic mechanisms. When substances released

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from damaged tissues, such as damaged cardiac parenchymal cells and the extracellular matrix, bind to and activate certain pattern-recognition receptors (PRRs) on cardiac fibroblasts and resident macrophages, they infiltrate leukocytes and activate a variety of inflammatory mediators through the innate immune system. This is known as the danger-associated molecular pattern (DAMP). The nuclear factor kappa B (NF-κB) pathway, mitogen-activated protein kinases (MAPK), and the NLR family pyrin domain containing protein 3 (NLRP3) inflammasome are the sites of downstream signals triggered by DAMP binding to PRR [31–33]. Numerous pro-inflammatory genes, including as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-10, and others, are expressed in response to activation of NF-κB and MAPK pathways [34, 35]. The junction molecule ASC and NLRP3 combine to create an inflammasome complex upon activation, which stimulates caspase-1 signaling. In order to initiate aseptic inflammatory characteristics, Caspase-1 cleaves pro-IL-1β and pro-IL-18 into their physiologically active counterparts. This leads to an increase in cardiomyocyte apoptosis and further cardiac damage [36]. In conclusion, Ca2+overload, peroxidation, andinflammation ntributetomyocardialcelldeathandplaycrucialrolesinthe devel- opment of myocardial I/R damage. Therefore, it is crucial to target the pathways of cell death in order to avoid or mitigate myocardial damage. Numerous regulatory processes, including as apoptosis, necrosis, pyroptosis, and autophagy, are involved in myocardial cell death. Apoptosis and autophagy preserve the integrity of the cell membrane, in contrast to necrosis and pyroptosis, which cause the membrane to break down. As a result, they do not trigger a pro-inflammatory reaction by releasing pro-inflammatory mediators or injury-related molecular patterns, which may cause extensive myocardial cell death. Targeting and controlling autophagy and apoptosis will thus probably reduce myocardial damage. Autophagy does not always lead to cell death, despite its strong correlation with it. Research has shown that the infarct size upon reperfusion may be decreased without resulting in cell death when autophagy is triggered by chloramphenicol succinate during myocardial I/R damage [37]. This implies that the function of auto After activation, phagy is dependent on the I/R stage. SIRT1 reduces myocardial damage

By altering a variety of histone and non-histone proteins and interacting with other variables, SIRT1 is known to regulate a number of pathophysiological processes, including oxidative stress, inflammation, and apoptosis during I/R (Fig. 2)[38]. Mice that had cardiac SIRT1-specific deletion showed higher levels of oxidative stress, inflammatory response, myocardial infarct size, and apoptosis rate in a mouse I/R model. On the other hand, SIRT1-specific overexpressed hearts showed significantly lower rates of oxidative stress, inflammation, myocardial infarct size, and apoptosis. This could be explained by the upregulation of antioxidant protein expression after SIRT1 stimulated the transcriptional activity of forkhead box transcription factor O1 (FOXO1), which in turn reduced the damage caused by oxidative stress to the heart [39]. By deacetylating nuclear factor E2-related factor 2 (Nrf2), scavenging excess reactive oxygen species, and enhancing the infarct size and amount of IR damage, SIRT1 may also increase the heart's antioxidant capacity [40]. Notably, the overexpression of SIRT1 in the heart induces oxidative stress in the myocardium, which may be associated with the sreguationofmitochondrialfunctionandmitochondrialbi ogenesisprograms [41]. This implies that SIRT1 may have a dose-dependent modulatory influence on the myocardial oxidative stress response. Notably, it is known that the nuclear factor kappa-B (NF-κB) signaling pathway regulates I/Rinjury in cardiac myocytes. SIRT1deacetylatesthe p65 subunit of NF-κB at lysine 310 and blocks its transcriptional activity, therebyinhibiting oxidativestressandinflammatoryresponses. Down-regulation of SIRT1 also boosted the amounts of TNF-αand pro- inflammatory molecules, such as IL-6 and IL-1β in cardiomyocytes, as wellasincreasedthesusceptibilityofmicetoI/Rinjury. Furthermore, SIRT1 agonists reduced the inflammatory response, inhibited the nucleotide oligomerization domain (NOD)-like receptor thermal protein domain linked to the activation of a protein kinase B (AKT) signaling-dependent protein 3 (NLRP3) inflammatory vesicles, and controlled glucose oxidative metabolism linked to pyru-vate dehydrogenase (PDH) in SIRT1 knockout myocardial I/R mice [42]. In order to decrease the extent of myocardial infarction, studies have shown that SIRT1 inhibits the NF-κB signaling pathway via NLRP3, lowers inflammatory cytokines, and enhances the production of glutathione (GSH) and superoxide dismutases (SODs) in I/R rats [43]. This implies that anti-inflammatory actions mediated by SIRT1 are essential for protecting against cardiac I/R damage. Similarly, protection against I/R damage depends on SIRT1-mediated anti-apoptotic actions in cardiac myocytes. Cardiomyocytes are protected from apoptosis in response to serum deprivation by SIRT1, which inhibits the p53 transcriptional activity in cardiomyocytes [44]. It is possible that the overexpression of DJ-1, consequent stimulation of SIRT1 activity, and inhibition of p53 acetylation in H9c2 cells are the mechanisms by which the SIRT1

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activator resveratrol prevents hypoxia/reoxygenation (H/R)-induced apoptosis in cardiomyocytes [45]. Additionally, SIRT1 inhibits cardiomyocyte apoptosis during I/R by promoting FOXO1 deacetylation and nuclear translocation and increasing the levels of B-cell lymphoma-2 (Bcl-2) and BCL-like X (Bcl-xL) [39]. Additionally, SIRT1 may improve myocardial I/R damage by upregulating the expression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which inhibits Bcl-2-associated X protein (Bax) and promotes Bcl-2 protein production [46, 47]. Along with apoptosis, the SIRT1-mediated p53/SLC7A11 pathway prevents myocardial apoptosis brought on by iron death during I/R. This is demonstrated by increased GSH levels, decreased iron accumulation, decreased lipid peroxidation, decreased reactive oxygen species, and enhanced myocardial infarction area and heart function [48].

2. AutophagyinmyocardialI/Rinjury

Autophagy is a critical metabolic pathway for cell survival. During autophagy,organellesormetabolicwastesareswallow

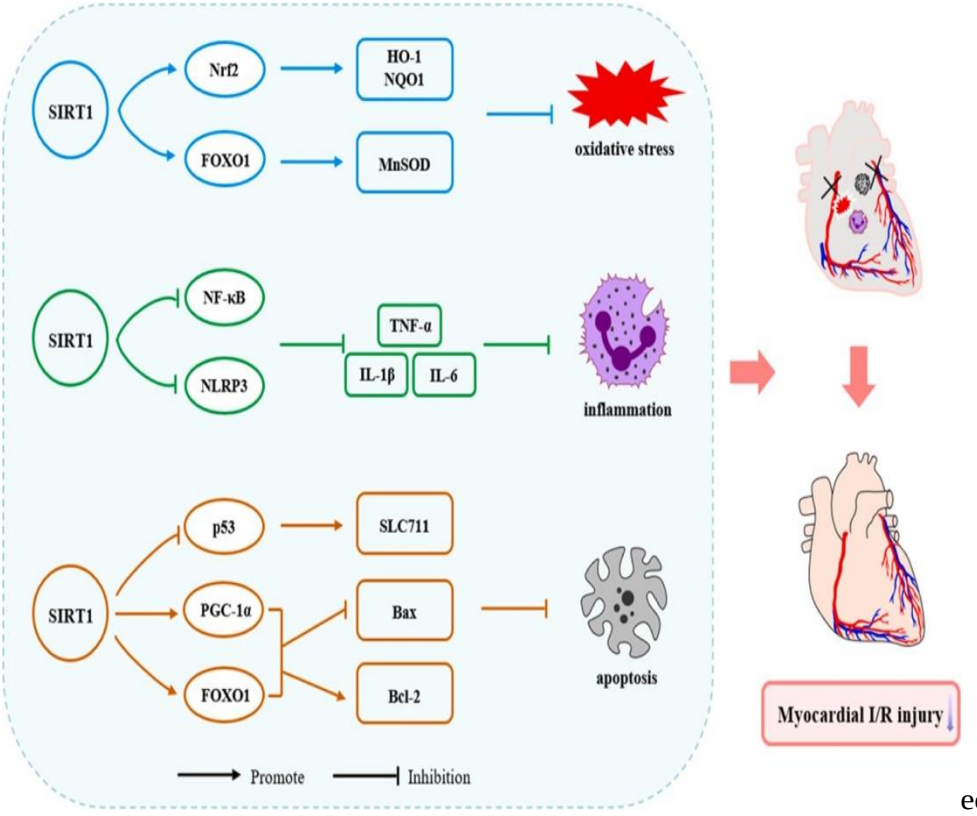

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Figure 2: SIRT1's mechanism for controlling cellular physiological and pathological processes to lessen myocardial I/R damage. SIRT1 reduces I/R damage by controlling oxidative stress via Nrf2 and FOXO1, inflammation through NF-κB and NLRP3, and apoptosis through p53, PGC-1α, and FOXO1.

In order to preserve cell homeostasis, the autophagosome joins forces with the lysosome to eliminate organelles or metabolic wastes [49, 50]. An essential physiological mechanism that preserves the heart's composition and functionality is autophagy [51]. Low amounts of stress trigger basal autophagy, which is believed to be a process for regulating the quality of proteins and organelles and preserving regular cellular homeostasis [52]. However, autophagy is triggered to manage cellular self-protection activities under stressful settings, such nutrition depletion or I/R. In organ-cultured fetal hearts, Sybersetal. detected autophagosomes harboring damaged organelles [53]. After 40 minutes of myocardial ischemia, Decker et al. observed a significant increase in cardiac autophagy triggered by reperfusion, as well as an increase in autophagic vesicles [54]. Additionally, during the acute ischemic phase, cardiac autophagy levels rose in mice and rats with I/R, and the degree of autophagy during reperfusion was noticeably higher than that during myocardial ischemia alone [55–58]. This implies that autophagy is triggered by cardiac ischemia and is subsequently boosted by

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ISSN 2347-2251 www.iajpb.com
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reperfusion. Autophagy has a dual function in myocardial I/R, according to a growing body of research. While excessive autophagy after reperfusion results in the depletion of intracellular components and eventually cell death, autophagy activation during the ischemic period eliminates excess metabolic waste and aids in maintaining cardiomyocyte viability [59]. Consequently, throughout these two phases, autophagy did not function consistently in the heart (Fig. 3). First, during the local myocardial ischemia phase, autophagy may serve as a source of energy. Reduced mitochondrial oxidative phosphorylation causes problems with mitochondrial metabolism, which in turn prevents ATP from being produced. Interestingly, when ATP levels

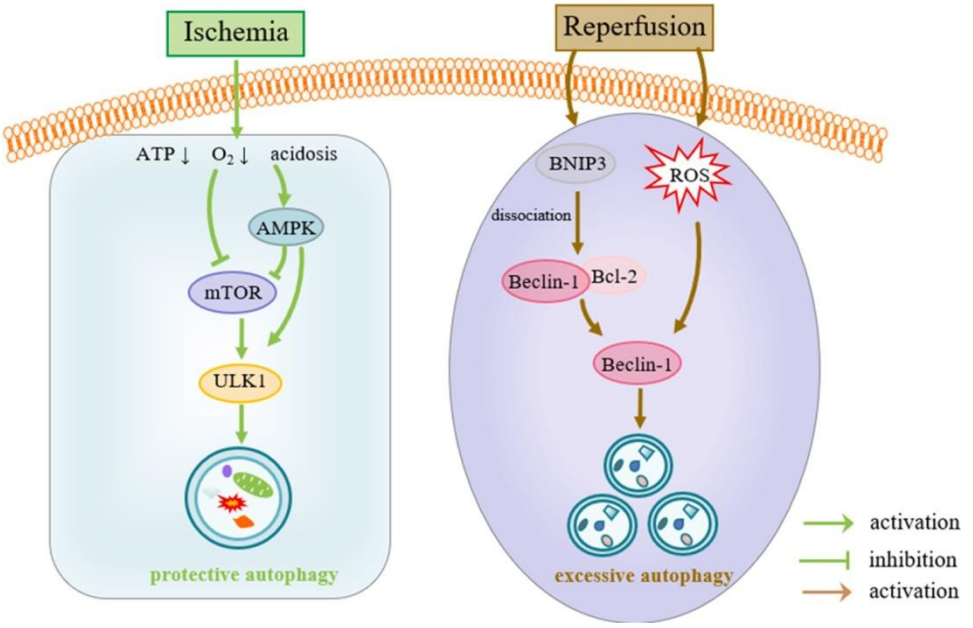

Fig. 3. Autophagy mechanisms in various myocardial ischemia-reperfusion stages. In the ischemia stage, ULK1 is activated by mTOR inhibition, which triggers protective autophagy. In the perfusion stage, Bcelin1 activation is the primary mechanism that activates excessive autophagy.

The energy sensor AMP-activated protein kinase (AMPK) is activated, which in turn triggers autophagy by upregulating the AMPK-mammalian target of rapamycin (mTORC1)-unc-51-like autophagy activating kinase 1 (ULK1) pathway [58]. In order to maintain ATP levels, glycolysis rises concurrently throughout this phase. This causes the buildup of hydrogen ions and lactic acid, which ultimately results in intracellular acidosis and the suppression of both glycolysis and the consumption of fatty acids. During ischemia, autophagy is triggered to release energy metabolites into the cytoplasm quickly. In order to compensate for the energy deficit during cardiac ischemia, autophagy eliminates metabolites to stop further damage and releases free fatty and amino acids into the cytoplasm, which subsequently produce ATP via the tricarboxylic acid cycle [60]. Loosetal discovered that moderate ischemia enhanced myocardial autophagy levels, preserved cell and mitochondrial membrane integrity, and postponed the beginning of irreversible cellular damage by imitating ischemia in H9C2 cells [61]. Second, damaged protein aggregates that are detrimental to the heart may be eliminated via autophagy. The operation of the cardiac ubiquitin-proteasome system is generally hindered during ischemia, including a decrease in proteasome activity and the capacity to break down proteins, which may result in the buildup of ubiquitinated and oxidized proteins [62]. However, during ischemia, autophagy activation eliminates misfolded polyubiquitinated protein aggregates, which reduces cardiomyocyte death and increases myocardial infarct size [63]. A third mechanism is that autophagy activation encourages damaged organelles to be removed and ROS levels in car-diomyocytes to be decreased. In ischemic cardiomyocytes, autophagy triggered by the HIF-1α/BNIP3 pathway eliminates broken-up damaged mitochondria and prevents ROS from leaking out and the opening of the mitochondrial permeability transition pore (MPTP) [64,65].

The autophagy process in the reperfusion phase is very different from the protective autophagy in the ischemia phase, and it seems to be harmful. The primary trigger for autophagy in the myocardium's ischemia phase is an energy crisis, which is partly resolved in the reperfusion phase as a result of the cardiomyocytes' subsequent supply of oxygen and nutrients. However, the primary

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trigger for autophagy during the reperfusion phase—which results in mitochondrial damage and fragmentation as well as the opening of the MPTP permeability transitionpore—is the excessive buildup of ROS [66]. Beclin-1 may be substantially upregulated in cardiomyocytes during the perfusion phase by ROS. While interventional treatment with the antioxidant N-2-mercapto propionyl glycine significantly inhibited Beclin-1 expression and scavenged the excess reactive oxygen species, lowering the autophagic flux and, in turn, the size of myocardial infarction, oxidative stress levels and Beclin-1 expression increased during myocardial perfusion [67]. Research has shown that Beclin-1-induced autophagy is an overabundance of autophagy. Beclin1 activation is required for the start of autophagy in early ischemia, but persistent Beclin-1 elevation during the reperfusion phase causes autophagy to become overactivated, removing vital proteins or organelles from cells, which causes cell dysfunction and induces autophagic death. However, autophagy during perfusion, which increases cell survival, was greatly decreased in myocardial cells when Beclin-1 was knocked down [68]. A crosstalk between Beclin-1 and Bcl-2 may be an additional mechanism by which perfusion damage results in Beclin-1-induced excessive autophagy, in addition to the ROS-Beclin-1 route. By dissociating the Beclin1 and Vps34 complexes, Bcl-2 binds to the BH3 structural domain of Beclin-1 and prevents the development of autophagosomes [69]. Reduced Bcl regulation is linked to Beclin-1-mediated excessive autophagy. -2 levels as the heart is reperfusing [70]. Furthermore, decreased Bcl-2 expression results in decreased Bcl-2/adenovirus E1B 19kDa-interactingprotein3 (BNIP3) expression, which is implicated in the stimulation of cardiomyocyte death and the upregulation of autophagy in myocardial I/R [71]. The negative impact of autophagy during the perfusion period may also be explained by ATG5-mediated autophagic cell death. Atg5 stimulates autophagic cell death by directly interacting with the Fas-associated protein with the death structure domain (FADD) via the death structural domain [72]. ATG5 is cleaved by upregulated calpain after reperfusion and transported to mitochondria, where it attaches to Bcl-XL and stimulates caspase activation and cytochrome c release, ultimately leading to apoptosis [73]. According to all of the aforementioned research, the survival of cardiomyocytes during reperfusion is hampered by the buildup of autophagosomes brought on by excessive autophagy [74]. Cardiomyocyte survival during reperfusion was hampered by Ma et al.'s findings that autophagic flux was impaired during perfusion and that autophagosome clearance in cardiomyocytes significantly decreased as reperfusion progressed. However, restoring autophagic flux could lessen the degree of oxidative stress and reperfusion injury [75]. Additionally, the disruption of autophagic flow by cleaving was made worse by highly active cal-pain. More severe myocardial perfusion damage is caused by ATG5 and LAMP2 [76]. Therefore, either activation of autophagy or inhibition of autophagic degradation may be the reason of the increase in autophagosomes after reperfusion damage.
According to distinct cellular pathways at each stage of myocardial I/Rinjury, autophagy may have either beneficial or detrimental consequences. Autophagic activity also influences these two opposing roles of autophagy. The protective mechanism of mild autophagy during the cardiac ischemic phase is in charge of supplying energy metabolic demands during ischemia/hypoxia and eliminating damaged organelles and protein aggregates to prevent further myocardial damage. Overautophagy during reperfusion causes intracellular components to degrade excessively, which worsens cardiomyocyte mortality. The molecular processes underlying the various functions of autophagy during ischemia and reperfusion remain unclear, despite the fact that the majority of recent research supports this theory. Therefore, further research is required to determine why autophagy may be beneficial or detrimental in a variety of experimental settings. It has been shown that other variables that affect the protective vs harmful effects of autophagy include the length and intensity of ischemia and reperfusion. While severe ischemia or reperfusion damage causes excessive autophagy and causes cell death, mild to moderate ischemia causes moderate levels of autophagy and has a car- dioprotective effect [66,77]. Thus, it may be said that autophagy is protective during the early ischemic phase of I/R damage, but it is detrimental during the reperfusion phase in the latter stages of I/R.

3. The connection between autophagy and SIRT1

Cellular stress conditions, including cellular hunger, heat and glucose deprivation, and other protein factors, influence the deacetylated protease SIRT1. SIRT1 targets a number of factors that control autophagy in the nucleus and cytoplasm, gene transcription, cell proliferation, differentiation, and DNA damage repair [78]. Research has shown that SIRT1-mediated autophagy plays a crucial role in stress tolerance, survival, and differentiation [79–81]. By acetylating microtubule-associated protein light chain 3 (LC3), forkhead box proteins (FOXOs), and autophagy-related proteins (ATGs), SIRT1 controls autophagy (Fig. 4). The SIRT1-FOXOs pathway

Transcription factors called FOXOs are essential for oxidative stress, DNA repair, apoptosis, and cell

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ISSN 2347-2251 www.iajpb.com
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proliferation [82]. FOXO1, FOXO3, FOXO4, and FOXO6 are members of the FOXO family in vivo. Post-translational modification of FOXO1 is a significant regulatory mechanism, and acetylation and deacetylation are critical in the control of autophagy [83,84]. SIRT1 has been shown in several studies to deacetylate FOXO1 and activate autophagy. SIRT1 expression rises in cardiac myocytes after dietary restriction, and

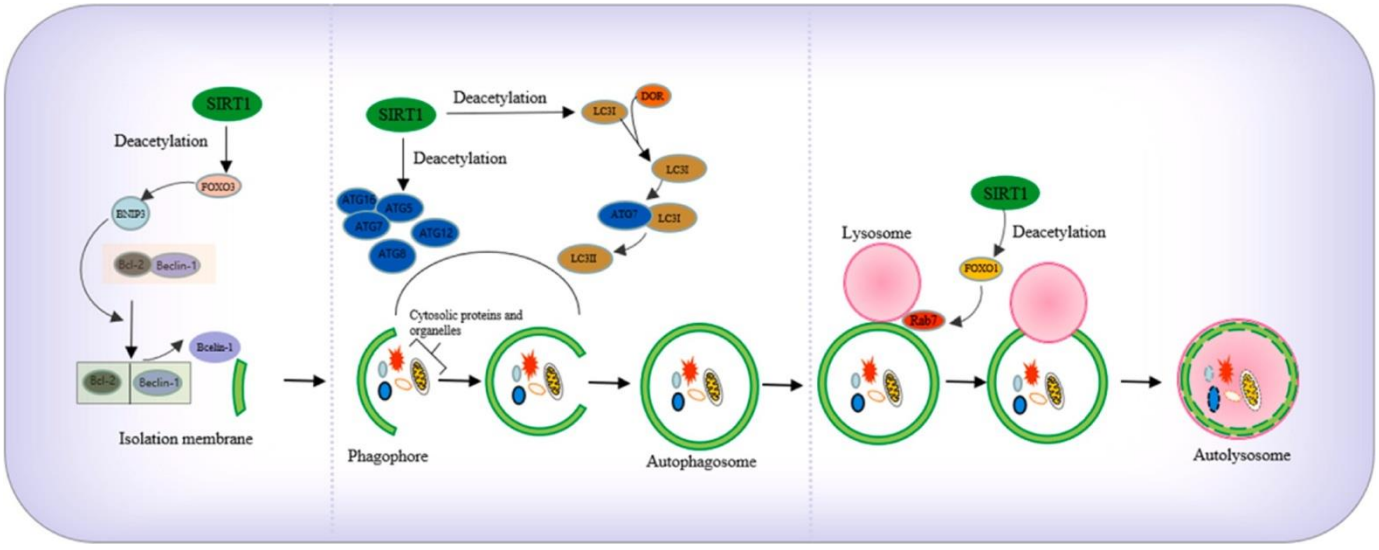

Fig.4. MechanismofSIRT1regulatingautophagy.SIRT1regulatesautophagythroughacetylationoftheATGsfamily,FOXOsfamily,andLC3.

enhanced nuclear translocation and associated protein activation in cardiomyocytes by deacetylating FOXO1. Furthermore, Ras-related protein in the brain 7 (Rab7), a crucial protein that enables late autophagosomal fusion with lysosomes, is expressed more when FOXO1 expression is elevated [85,86]. In the myocardium of diabetic mice, long-term resveratrol therapy improves oxidative damage, enhances autophagic flux, lowers p62 expression, and boosts SIRT1, FOXO1, and Rab7 expression. Resveratrol enhanced the autophagic flow in H2C9 cardiomyocytes by activating SIRT1, which in turn increased the binding of the Rab7 promoter region to FOXO1DNA, according to further in-vitro tests [87]. Furthermore, Wuetal. demonstrated that resveratrol increases autophagic flux, boosts Rab7 expression, decreases p62 accumulation, and activates the SIRT1/FOXO1 pathway in vascular endothelial cells [88]. Therefore, our findings suggest that the SIRT1-FOXO1-Rab7 axis must be activated in order to induce autophagy.

Additionally, SIRT1 may directly interact with FOXO3 to cause its degradation [89]. By connecting to the BNIP3 promoter, deacetylated FOXO3 increases the production of BNIP3, which in turn causes autophagy by breaking down the Bcl-2-beclin-1 complex and encouraging its dissociation [90]. higher SIRT1 expression was followed by higher FOXO3deacetylation and increased expression of its substrate, BNIP3, in the fluorine-treated MC3T3-E1 osteoblast cell line. This improved the autophagic flux and reduced fluorine-induced apoptosis. This implies that the FOXO3/Bnip3 pathway is how SIRT1 stimulates autophagy [91]. The SIRT1-ATG pathway

Autophagy activation depends on SIRT1-mediated deacetylation of ATGs (e.g., ATG5, ATG7, ATG8, and ATG12), and SIRT1 regulates the maturation and elongation of autophagosomes via this deacetylation activity. Although autophagy was not completely triggered in SIRT1 mutant mice during fasting, transient overexpression of SIRT1 increased the baseline rate of autophagy. The E1A binding protein p300 (EP300) inhibits the ATG5-ATG12-ATG16 complex by acetylating ATG5, ATG7, and ATG12 in nutrient-rich environments. This stops autophagosome elongation. On the other hand, SIRT1 directly deacetylates ATG5, ATG7, and ATG12 in a way that is reliant on NAD during hunger. This, in turn, triggers the formation of the ATG5-ATG12-ATG16 complex and aids in the elongation of autophagic vesicles [80,92]. Deacetylation of SIRT1 post-translationally may thus be a crucial route for the induction of

of autophagy. Additionally, Suzuki et al. discovered that fluoride treatment increases the expression of SIRT1 and its deacetylation activity in cells, which in turn

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ISSN 2347-2251 www.iajpb.com
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raises the amounts of ATG5, ATG7, and ATG8 transcripts and proteins. This activates autophagy and stops cells from being exposed to fluoride [81]. The SIRT1-LC3 pathway

In the regulation of autophagy, autophagosome formation, cargo recruitment, and autophagosome fusion, LC3 is one of the most important proteins. A ubiquitin-like coupling pathway connects LC3 to lipid phosphatidyletha-nolamine (PE) via ATG3 and ATG7 [93,94]. The cytoplasm and nucleus are where LC3 is mostly expressed. In the nucleus, soluble LC3 is transferred to the cytoplasm, transformed into lipidated LC3, and embedded in the autophagic membrane, where it participates in the production of autophagosomes [95]. It was initially shown by Huang et al. that SIRT1 causes autophagy during famine by quickly deacetylating and activating nuclear LC3. SIRT1 deacetylates nuclear LC3I at the K49 and K51 locations when cells are starved. Deacetylated LC3I interacts with deltaopioid receptor (DOR) proteins and enables LC3I to co-nucleate with DOR proteins to enter the cytoplasm. There, it interacts with ATG7 and forms LC3II with PE, which is then inserted into the autophagic pre-membranetoselectively target cargo [96].

3. SIRT1-mediated autophagy's mechanism and use in myocardial I/R damage

Autophagy contributes to myocardial I/R damage in two ways. Cardiomyocytes benefit from moderate autophagy during the ischemia phase, but myocardial damage is worsened by excessive autophagy during the reperfusion phase [97]. As previously mentioned, SIRT1 controls autophagy via a number of mechanisms, including the deacetylation of LC3, ATGs, and FOXOs. According to recent research, SIRT1-mediated autophagy has distinct functions depending on the degree of myocardial I/R damage. The relationship between SIRT1 and autophagic signaling pathways in cardiac I/R damage and associated molecular pharmacological applications is then covered (Fig. 5, Table 1[98]). The Ischemic Stage

SIRT1-mediatedautophagyprotectsagainstmyocardialischemia.

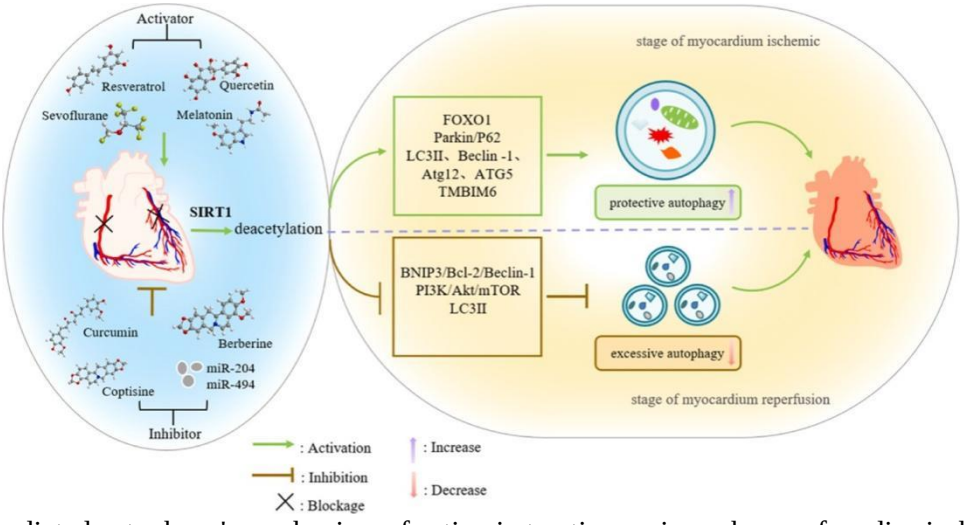

Figure 5: SIRT1-mediated autophagy's mechanism of action in treating various phases of cardiac ischemia-reperfusion. Protective autophagy is promoted and myocardial ischemia damage is lessened in the myocardial ischemic stage by sevoflurane, quercetin, melatonin, and resveratrol-activated FOXO1, Parkin/p62, TMBIM6, and Bnip3/ATG5/LC3II signaling pathways. By suppressing the expression of SIRT1, Coptisine, curcumin, Berberine, miR-204, and miR-494 prevent excessive autophagy and lessen damage during cardiac reperfusion by inhibiting the BNIP3/Bcl-2/Beclin-1, PI3K/Akt/mTOR, and LC3II pathways during the ischemia reperfusion stage.

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ISSN 2347-2251 www.iajpb.com
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Table1

DifferentdrugsprotectI/R-induceddamagebyregulatingautophagythroughSIRT1.

Name	Typeof study	Studydesign	EffectonSIRT1mediatedautophagy	Researchsummary	Refs.
Resveratrol	In-vivo	MousemyocardialI/R,dosingbeforeI/R	Promote	p-AMPK,SIRT1,p-FOXO1↑ LC3B,Beclin—1,Atg12↑ p62,TNF-α,IL-1β↓ Cardiomyocyteapoptosisrate↓ Areaofmyocardialinfarction↓	[104]
	In-vitro	PrimarycardiomyocytesH/R,dosingbeforeH/R	Promote	SIRT1,FOXO1,SOD,PINK1↑Parkin, LC3II ↑ MDA↓	
Sevoflurane	In-vivo	Limbischemiareperfusion,dosingafterI/R	Promote	SIRT1,LC3II↑ Cardiomyocyteapoptosisrate↓	[108]
Quercetin	In-vitro	HumancardiomyocytesH/R,dosingbeforeH/R	Promote	SIRT1,LC3II,Beclin-1,Bcl-2↑ SOD,CAT,GSH,GPX↑ Cardiomyocyteapoptosisrate↓ Cellviability↑	[111]
Melatonin	In-vivo	MousemyocardialI/R,dosingbeforeI/R	Promote	Mst1,SIRT1,Beclin1,LC3II↑ p62↓,ROS↓ Cardiomyocyteapoptosisrate↓	[113]
Coptisine	In-vitro	H2C9cardiomyocytesH/R,dosingafterhypoxia,before reoxygenation	Inhibit	SIRT1,Beclin1,LC3II↓ Caspase-3↓ Cardiomyocyteapoptosisrate↓	[119]
Curcumin	In-vitro	H2C9cardiomyocytesH/R,dosingbeforeH/R	Inhibit	SIRT1,BNIP3,Bcl-2,Beclin-1↓ LC3II/LC3I↓ Cardiomyocyteapoptosisrate↓	[124]
Berberine	In-vivo	MousemyocardialI/R,dosing15minbeforereperfusion	Inhibit	SIRT1,Beclin-1,BNIP3↓ Cardiomyocyteapoptosisrate↓ Areaofmyocardialinfarction↓	[128]

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ISSN 2347-2251 www.iajpb.com
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miR-204	In-vitro	H2C9cardiomyocytes	H/R,dosingafter	Inhibitor	SIRT1,Beclin1,LC3II/LC3I↓ Cardiomyocyteapoptosis rate↓ [129]
miR-494	In-vitro	H2C9cardiomyocytes	H/R,dosingafter	Inhibitor	SIRT1↓ p-PI3K,p-AKT,p-mTOR↓ Cardiomyocyteapoptosis rate↓ [130]

One of the initial studies discovered that the hearts of wild-type mice that had received acute ischemia in the first window had higher levels of SIRT1 deacetylation at lysine sites. It also observed that autophagy-related indices in SIRT1 downstream targets were downregulated. While SIRT1-specific knockdown dramatically reversed the above effects, SIRT1 over-expression further increased autophagy levels and had protective effects on cardiac structure and function, indicating that SIRT1lysinedeacetylation-induced autophagy is necessary for protection against acute myocardial ischemia injuries [23]. Thus, enhancing protective autophagy during ischemia by targeting SIRT1 may be a useful therapeutic approach. The applications and molecular mechanisms of related small-molecule medications are discussed in the sections that follow. Resveratrol
Resveratrol (Fig. 6A) is a naturally occurring polyphenol called stilbene.

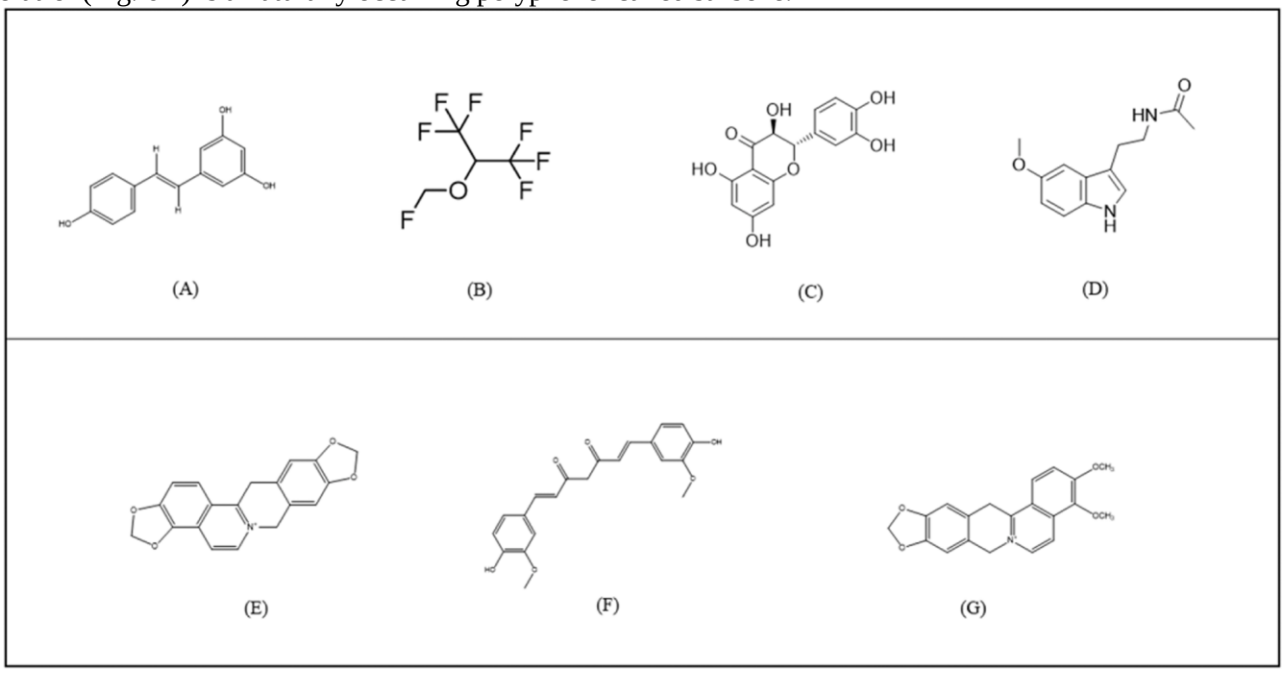

Fig.6. Chemicalstructureofsmallmoleculedrugsforthetreatmentof I/Rinjury.

Restoratrol (A), sevoflurane (B), quercetin (C), melatonin (D), copolysine (E), curcumin (F), and berberine (G). Veratrum grandiflorum, grapes, pea-nuts, blueberries, pistachios, and strawberries are among the plant extracts that contain it [99]. Its chemical structure consists of a double bond forcis-or trans-isomerization and two phenol rings at either end of the double bond [100], which allow it to prolong its life through caloric restriction (dietary restriction) [101]. Recent clinical studies have demonstrated that resveratrol has a variety of protective cardiovascular effects that are primarily attained by lowering inflammation and oxidative stress [102].

One of the main causes of cardiomyocyte injury during I/R is the overproduction of reactive oxygen species (ROS) in the mitochondria. Thus, Zhengetal. developed an in-vitroH/R model to assess whether resveratrol could enhance mitochondrial antioxidant function during the onset of I/R. They discovered that resveratrol-treated primary cardiomyocytes exhibited increased expression of SIRT1-FOXO1, mitochondrial autophagic PTEN-induced kinase 1 (PINK1), Parkin

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ring-between-ring (RBR) E3 ubiquitin-protein ligase (Parkin), and LC3II protein, as well as improved binding of p62 to Parkin, increased the SOD content, and decreased the MDA content [103]. This implies that resveratrol improved the mitochondrial antioxidant system and increased autophagy in a dose-dependent manner. In addition, by injecting resveratrol into MI/RI model mice, it promoted the expression of autophagy-related proteins LC3II, Beclin-1, and ATG12, decreased TNF-α and IL-1β to lessen the inflammatory response, and decreased ROS to improve the oxidative stress, as well as reduce cardiomyocyte apoptosis and the size of the infarct. In vitro H/R treatment of cardiomyocytes and low expression of AMPK, SIRT1, and FOXO1 in H9c2 cells further confirmed that AMPK/SIRT1-FOXO1-activated autophagy played the same roles as in vivo [104]. However, it is still unclear whether AMPK and SIRT1 have a mutual regulation mechanism.

Sevoflurane

A highly fluorinated methylisopropylether, sevoflurane (Fig. 6B) is a volatile anesthetic with poor solubility that has anti-inflammatory and antioxidant properties [105]. Similar to ischemic preconditioning, sevoflurane administered either before or after myocardial I/R reduces oxidative stress, myocardial infarct size, and apoptosis brought on by hypoxia/reoxygenation [106]. Sevoflurane therapy suppressed myocardial apoptosis in cardiac tissue, decreased infarct size, elevated SIRT1 protein expression, and decreased miR-155 expression [107]. Fanet al. induced myocardial damage in rats using limb I/R and found that the injured myocardium had higher levels of autophagy. SIRT1 inhibitors reversed the effects of sevoflurane therapy, which raised SIRT1 expression, which in turn deacetylated LC3, further promoted autophagy, increased the quantity and size of autophagic vesicles, and reduced myocardial damage [108].

Quercetin

A naturally occurring antioxidant present in a variety of fruits and vegetables, quercetin (Fig. 6C) has minimal toxicity both in vitro and in vivo, may scavenge free radicals, and has immunomodulatory, anti-inflammatory, and antioxidant properties that can prevent or guard against cardiovascular illnesses [109,110]. Excessive ROS impeded autophagy and mitochondrial function in a human cardiomyocyte model of H/R-simulated I/R damage, which eventually resulted in cardiomyocyte demise. By promoting SIRT1 expression, quercetin pretreatment increased the mRNA and protein expression of transmembrane BAX inactivator 1 motif-containing 6 (TMBIM6), increased cell autophagy, and improved antioxidant enzyme activity. Oxidative stress damage was prevented, cardiomyocyte susceptibility to H/R was improved, and SIRT1 was downregulated using siRNA to validate the crucial regulatory role of SIRT1 [111].

Melatonin

The pineal gland secretes melatonin (Fig. 6D), a neuroendocrine hormone that controls the hypothalamic-pituitary axis via the hypothalamus. Its direct scavenging of free radicals, indirect antioxidant activity, and anti-inflammatory ability provide it cardioprotective qualities [112]. In myocardial infarcted mouse hearts, melatonin is known to significantly inhibit macrophagestimulating 1 (Mst1) phosphorylation. This, in turn, has been shown to improve ischemic symptoms, regulate mitochondrial integrity, enhance autophagy, decrease car-diomyocyte apoptosis and ROS production, and upregulate SIRT1 expression [113]. By inhibiting Mst1 and SIRT1, research has shown that the Mst1/SIRT1 signaling pathway is a mechanistic target for melatonin therapy. Furthermore, by promoting the expression of Beclin-1 and ATG5 and the conversion of LC3I to LC3II, myocardin-related transcription factor A (MRTF-A) works in concert with SIRT1 to alleviate myocardial ischemia-induced cardiac damage by increasing autophagy and decreasing NLRP3 inflammatory vesicle activity [114]. This implies that the therapeutic effects of melatonin depend on SIRT1 but are not exclusive to it, and that more research is necessary to understand the more downstream or synergistic signaling pathways.

stage of reperfusion

Excessive autophagy worsens myocardial I/R damage during the perfusion period and may be mediated by SIRT1. Therefore, stopping SIRT1-induced excessive autophagy during reperfusion may help to preserve cardiac function and lower cardiomyocyte death. While SIRT1 knockdown significantly inhibited excessive autophagy and attenuated cardiomyocyte H/R injury, thrombin expression was found to be elevated in a car-

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diomyocyte H/R model, which enhanced H/R upregulation of SIRT1 expression and promoted the overexpression of Beclin-1 and LC3II proteins [115]. We discovered that during the reperfusion phase, small molecules like scoposine, curcumin, berberine, and certain miRNAs were involved in controlling the SIRT1-autophagy axis, resulting in a cardioprotective effect; the precise mechanism is covered below.

Coptisine

The yellow lily of the valley contains coptisine (Fig. 6E), a naturally occurring isoquinolinealkaloid with a variety of biological activities, such as antiviral, antibacterial, and anti-cancer properties [116,117]. Coptisine provides cardioprotection in myocardial infarction and I/R models because of its potent antioxidant action, preservation of cell membrane integrity, amelioration of mitochondrial respiratory failure, and reduction of inflammatory responses and cardiomyocyte apoptosis [118]. Conversely, coptisine treatment inhibited cardiomyocyte autophagy and apoptosis and increased cell survival by decreasing the protein expression of SIRT1, Beclin-1, LC3II, and caspase-3, most likely by blocking the SIRT1/Beclin-1 autophagy axis [119]. The expression of SIRT1, caspase-3, and autophagy markers Beclin-1 and LC3 significantly increased in the NaS2O4-induced H/R model of cardiomyocytes.

Curcumin

Comprising 77% diferuloylmethane, 18% demethoxycurcumin, and 5% bisdemethoxycurcumin, curcumin (Fig. 6F) is a naturally occurring polyphenolic compound derived from the rhizome of turmeric. Curcumin is relatively safe and non-toxic and has a variety of potential biological effects, including anti-inflammatory, antioxidant, anti-cancer, and cardiovascular protection effects [120,121]. According to earlier research, curcumin promotes the SIRT1-FOXO1 axis, which lowers myocardial oxidative stress levels and attenuates myocardial apoptosis in diabetic rats [122]. Tetrahydrocurcumin, a curcumin metabolite, partially activated the PI3K/Akt/mTOR pathway during H/R-induced excessive autophagy and apoptosis in a cardiomyocyte H/R model, decreased the formation of H/R-induced excessive autophagosomes, and effectively decreased Beclin-1 expression and the LC3II/LC3Iratio [123]. The expressions of SIRT1, BNIP3, and Beclin-1 were found to be elevated, Bcl-2 expression was decreased, and cardiomyocyte survival was decreased in another H/R model of H2C9 myocardium that simulated myocardial I/Rinjury. This may be related to the accelerated dissociation of the Beclin-1/Bcl-2 complex following SIRT1 activation of BNIP3, which in turn caused the over-activation of autophagy. Curcumin treatment of H/R cardiomyocytes, on the other hand, blocked excessive autophagy by inhibiting the expression of SIRT1 and reducing the expression of autophagy-related proteins. This suggests that curcumin may have a protective impact on cardiomyocytes via the SIRT1/BNIP3/Bcl-2/Beclin-1 autophagy axis [124]. Furthermore, curcumin's regulatory effects on SIRT1 may change depending on the myocardial model, and further research is needed to determine the regulatory mechanisms at play.

Berberine

Berberine(Fig.6G)isanisoquinolinealkaloidthatcanbeextracted from a range of plants, including Hydrastis canadiens, Cortex phyllo dendrites, and Rhizoma coptidis. Previous studies have reported the significant beneficial effects of berberine in various disease models, including the heart, kidney, brain, muscle, and liver, with particular importance for the treatment of cardiovascular diseases[125,126]. BerberineinducesmiR-26b-5pandblocksthePTGS2/MAPKpathwayin I/R myocardium, inhibiting inflammatory responses and improving cardiac histology [127]. In reperfusion-injured mouse myocardium, autophagy ishighly induced, accompanied by elevated SIRT1 expression. Treatment with berberine decreases myocardial autophagy activation, improves cardiac function, and decreases the size of myocardial infarcts. This is in line with in-vivo research that found that in a H/R-simulated cardiomyocyte reperfusion model, SIRT1, BNIP3, and beclin-1 levels were much higher. Treatment with berberine decreased cardiomyocyte apoptosis and inhibited excessive autophagy mediated by the SIRT1/BNIP3/Beclin-1 axis [128].

miRNAs

MicroRNA (miR) may be a significant therapeutic target for subsequent I/R injury in addition to small molecules like coptisine, curcumin, and berberine that

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may be viable candidates for the treatment of myocardial I/R injury. Qiu et al. discovered that following 12 hours of hypoxia and 24 hours of reoxygenation, along with cardiomyocyte apoptosis, miR-204 expression was markedly downregulated in H2C9 cardiomyocytes. In contrast, miR-204 overexpression significantly inhibited the expression of SIRT1 and Beclin-1 and the conversion of LC3ItoLC3II,ameliorating H/R-induced apoptosis. In contrast, rescue experiments with SIRT1 overexpression showed increased autophagy and apoptosis, suggesting that the activation of excessive autophagy in H/R cardiomyocytes is achieved through the miR-204/SIRT1 pathway [129]. Similarly, H2C9 cardiomyocytes in another research observed that miR-494 expression levels were downregulated after 12h of hypoxia and 3h of reoxygenation, associated with increased SIRT1 expres- sion and autophagy. miR-494 overexpression decreased H/R-induced excessive autophagy and apoptosis in cardiomyocytes, wh ereas miR-494 inhibition had the reverse impact. Additionally, in H2C9 cells exposed to H/R and transfected with an inhibitor of miR-494, SIRT1 knockdown markedly elevated the phosphorylation levels of PI3K, AKT, and mTOR, hence suppressing autophagy. This implies that miR-494 directly targets the SIRT1/PI3-K/AKT/mTOR pathway to prevent H/R-induced cardiomyocyte apoptosis and autophagy [130]. Protective autophagy was the primary focus of the previously mentioned studies. during myocardial ischemia and excessive autophagy after reperfusion, although other research has shown that myocardial I/R injury is also made worse by reduced autophagy levels brought on by autophagic damage [131]. Following myocardial I/R injury in diabetic rats, the expression of histone deacetylase 3 (HDAC3) was upregulated, SIRT1 and brain and muscle Arnt-like protein 1 (Bmal1) was downregulated, and autophagy levels were decreased. Targeting the HDAC3/SIRT1/Bmal1 axis to activate autophagy may be a novel approach to attenuating myocardial I/R injury, as treatment with the HDAC3 inhibitor RGFP 966 and SIRT1 agonist SRIT1 720 significantly decreased myocardial I/R injury by restoring Bmal1-mediated autophagy. Additionally, H/R treatment of cardiomyocytes increased the expression of miR-217-5p in cells, reduced the expression of SIRT1, LC3II, and Bcl-2, and increased ROS and apoptotic cells. Restoring SIRT1-mediated autophagy and reverses cell damage caused by H/R. This implies that miR-217-5-p/SIRT1 could be a target for autophagy damage and mitochondrial function recovery [132].

3. Other treatments for ischemia-reperfusion injury of the heart

Finding effective therapeutic strategies to combat myocardial I/R injury is of paramount importance. General treatment of myocardial I/R includes nonpharmacologic (e.g., ischemic aftercare, remote ischemic conditioning, hyperbaric oxygen, and hypothermia) and pharmacologic therapies [133]. There is variability in the prognosis of non- pharmacologic treatments, whereas pharmacologic treatments are limited by target shortages and drug side effects. Therefore, the devel- opment of novel drug delivery systems may provide new ideas and av- enues for the treatment of myocardial I/R. In the following part, we will first quickly outline the present conventional pharmacological therapy, fol- lowed by a detailed review of the development and applicati on of novel drug delivery methods in recent years.

Conventional therapies for myocardial ischemia-reperfusion injury

Currently, most clinical and relevant animal research administra- tions are in the form of water-soluble drugs. Based on the mechanism of myocardial I/R injury, common therapeutic targets currently include oxidative stress, inflammation, mitochondrial dysfunction, autophagy, and so on. Anti-inflammatory antioxidant drugs commonly used in clinical studies include melatonin, dexmedetomidine (DEX), and curcumin, which exert potent cardioprotective effects in myocardial I/R by modulating inflammation and scavenging various ROS. Clinical evidence indicates that DEX attenuates oxidative stress and melatonin supplementation effectively decreased plasma levels of cardiac troponin-I (CTnI), interleukin-1β (IL-1β), inducible nitric oxide synthase (iNOS), and caspase-3 enzymes in patients with myocardial I/R [134].

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Animal experiments and ischemic myocardial injury in patients [135] furtherdemonstratedthatDEXreducedcardiomyocyteapoptosisand
I/R damage via autophagy upregulation, ROS decrease, and HMGB1 pathway suppression of inflammatory response [136]. Curcumin also lowers the expression of pro-inflammatory cytokines during extracorporeal circulatory surgery.
and substantially decreases myocardial infarction rates inconsecutive individuals having coronary artery bypass grafting [137], and cur-cuminexertsitscardioprotectiveeffectsbymodulatingoxidativestress,
inflammation-relatedpathways[120].
It is believed that a major factor in I/R is myocardial mitochondrial dysfunction caused by the opening of the mitochondrial permeability transition pore (MPTP) [138]. Schaffer et al. provided a thorough summary of the protective impact of softaurine in myocardial I/R, which decreases MPTP opening by activating the Akt-dependent protective signaling pathway, lowering ROS overproduction in the respiratory chain, and preventing calcium overload [139]. Moreover, cyclophilin D (CyPD) promotes MPTP. Statins also activate mitochondrial ATP-sensitive potassium channels (mitoKATP), inhibit the phosphorylation of uncoupling proteins and glycogen synthase kinase 3β (GSK3β), delay the opening of MPTP, decrease the production of ROS, improve mitochondrial swelling anddy function, and ultimately reduce the size of the infarct [140].
openingbyenhancingitscalciumsensitivity[141], whereascyclo-sporinA(CsA)cantargetCyP-Dtoprotectcardiomyocytes.However,
It is challenging to ascertain if local CsA concentrations are beyond the therapeutic threshold since cyclosporine has some toxicity and the effects of intravenous CsA doses have been inconsistently shown in inclinical investigations [142].
Relevant medications that target the SIRT1-autophagy axis for the treatment of myocardial I/R have already been compiled, and considering the dual function of autophagy in myocardial I/R, there are several other medications.

focusing on autophagy. A protective effect against myocardial injury may result from adaptive induction of autophagy during the myocardial ischemic phase. Previous research has shown that certain medications, including alliin [143], coenzyme Q10 (CQ10) [144], spermine [145], chloramphenicol succinate (CAPS) [146], low-dose resveratrol [147], etc., can increase autophagy activity by decreasing apoptosis and alleviating myocardial ischemic damage. Trimetazidine (TMZ) [148], prami-pexole (PPX) [149], rapamycin [150], acetylcholine (ACh) [151], γ-tocotrienol [152], and other medications can act on AMPK to inhibit mTOR phosphorylation, increase autophagy levels, and exert their car-dioprotective effects. On the other hand, myocardial I/Rinjury may be lessened by a number of therapeutic medications that either block excessive autophagy or improve defective autophagic flow during the perfusion period. One important factor in the start of excessive autophagy is the persistent televation of Beclin-1. Tetramethylprazine (TMP) [153], anti-thrombin III (AT) [154], berbamine [155], rradioprotective 105kDa protein (RP105) [156], 17-Methoxyl-7hydroxy-benzene-furanchalcone (MHBFC) [157], sevofurane [158], pyrrolidine dithiocarbamate (PDTC) [159], and other medications were found to increase Bcl-2 expression or scavenge excess ROS to inhibit Beclin-1-dependent autophagy induced by reperfusion injury. Additionally, administration of Urolithin B (UB) [160], hesperidin [161], choline [162], and Danshensu (DSS) [163] directly blocked the initiation of autophagy through activation of either the AMPK/mTOR or the PI3K/Akt/mTOR pathway, which in turn reduced the autophagic death of cardiomyocytes. Excessive autophagosome buildup is another effect of impaired autophagic flow. In I/R-injured myocardium, calreticulin (CRT) may enhance Lamp2 expression and encourage autophagosome disintegration and autophagosomal lysosomal fusion to ameliorate defective autophagosome clearance [164]. In order to cure reperfusion damage, sevoflurane postconditioning (SPC) therapy stimulated the NOS/NO pathway, which lowers MPTP opening and cytochrome c release and restores decreased autophagic flow [165]. These medications, which are water molecules, are described above.
soluble drugs, usually exhibit poor water solubility,metastasis, bioavailability, short half-life, and side effects, thus limiting their clin- ical application and

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even leading to a high incidence of adverse cardiovascularevents[166].Thereforeexploringmoreefficientandprecise drugdeliverymodalitiesisessentialtoimprovethetherapeuticoutcome of myocardial I/R injury.

Cardiovascular ischemia-reperfusion injury: new options

The reticuloendothelial system (RES), the mononuclear phagocyte system, and lysosomal degradation are just a few of the complex biological barriers that drugs used to treat I/R injury typically have to overcome in order to reach their corresponding target of action. In contrast to traditional small molecule water-soluble drugs, drug delivery via nanocarriers can get past these barriers, communicate with target cell membranes with ease, target and deliver therapeutic compounds specifically, improve drug utilization, reduce side effects, and ultimately maximize therapeutic efficacy [167]. Synthetic polymer nanoparticles (NPs), inorganic NPs, liposomes, and extracellular vesicles (Evs) are the most sophisticated nanocarriers presently used to treat myocardial I/R damage (Fig. 7).

NPs of polymers

Reactive chemicals adsorbed inside or on the surface of polymer nuclei are captured by polymer nanoparticles (NPs), which are particles with sizes ranging from 1 to 1000 nm. Because polymer nanoparticles may preserve drug bioactivity, biocompatibility, degradability, etc., they are often used as drug carriers in preclinical and clinical research [168]. The most common formsofPolymerNPsarenanocapsulesandnanospheres.Nanocapsules consist of an oily core, where the drug is dissolved, surrounded by a polymer shell capable of controlling the release of the drug from the core.Nanospheresarecontinuousnetworksinwhichthedrugcanbe

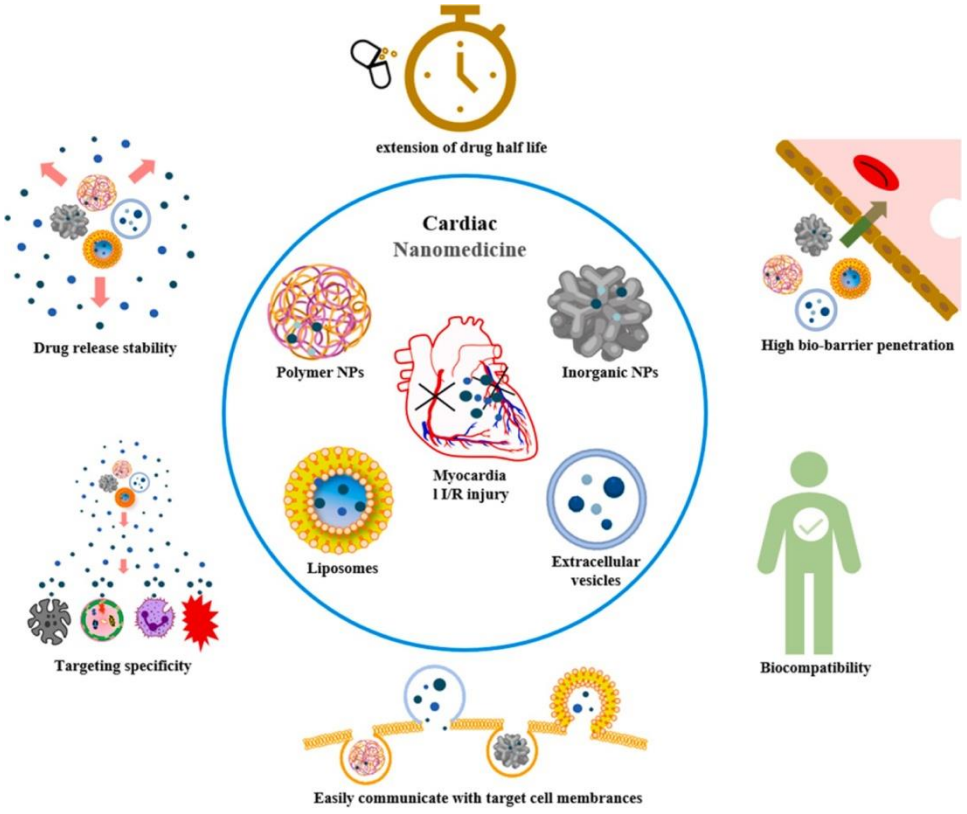

Fig.7. Advantagesofnanocarriersin drugdeliveryfor myocardialI/R treatment.

retained on their surface after being absorbed [169]. For the detection and treatment of cardiac IRI, polymer

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nanoparticles (NPs) have strong drug delivery capabilities. Tissue plasminogen activator (tPA) has limited effectiveness against myocardial damage due to its short half-life and poor targeting. created a biomimetic nanoparticle (PTPN) that was encapsulated by platelet membranes and comprised of a thrombus microenvironment-responsive phenolboronic acid (PBA) nanocarrier, the antioxidant molecule proto-catechualdehyde (PC), and tPA. Platelet membranes' capacity to target thrombus allows PTP to stick to injured endothelial cells, which subsequently degrade in the presence of microacidic conditions, reopening the infarcted artery during ischemia. However, free PCs generated by PTPN disintegration inhibited blood perfusion-induced ROS, preserving cardiac mitochondrial function from I/Rinjury [170]. Exenatide's short half-life of 9.5 hours in circulating blood limits its therapeutic applicability since it requires repeated injections, although it may reduce I/Rinjury by modifying cardiomyocyte metabolism [171]. As the nanocarrier for exenatide, poly (L-lysine)-poly(ethyleneglycol)-poly(L-lysine)(PLL-PEG-PLL)NPs increase the drug's circulation lifespan in vivo and extend its pharmacological effects [172]. Huang et al. created a redox-responsive and emissive TPE-ss covalent organic framework (COF) nanocarrier that can effectively load and deliver picloram. After injecting the TPE-ss COF carrier into the MI/R model for five minutes via the tail vein, it significantly reduces cardiomyocyte ischemia and apoptosis caused by myocardial I/R injury and improves cardiomyocyte viability and cardiac function [173]. Furthermore, resveratrol (RES) was transported by methoxypoly (ethylene glycol)-b-oligomerization (D, L-Leucine) (mPEG-b-O (D, L-Leu)) NP, which significantly extended the circulating half-life and time of release of RES and significantly improved its anti-myocardial I/R injury effect when compared to free RES [174]. Non-organic NPs

Because of their superior chemical and thermal stability over organic nanoparticles, inorganic nanoparticles are simpler to utilize, store, and transport under harsh conditions [175]. Because of their unique optical properties, electrical conductivity, magnetism, catalytic properties, controllable size, and good biocompatibility, inorganic nanoparticles (NPs) are widely used in the pharmaceutical industry. They can be synthesized from a variety of raw materials, primarily metals, semiconductor materials, and metal oxides. Every inorganic NP has a characteristic core and shell structure, with the shell blocking the core from binding to biomolecules like proteins, oligonucleotides, and antibodies or from chemically reacting with the external environment. These days, silicon-based inorganic nanoparticles, iron-based inorganic nanoparticles, carbon-based inorganic nanoparticles, and others are often used [176,177].

For instance, quercetin's low water solubility, short half-life, and poor bioavailability for clinical applications may be mitigated by its delivery via silicananoparticles (Q-MSNs). The application of Q-MSNs more successfully inhibited the level of oxidative stress and apoptosis of cardiomyocytes, decreased the size of myocardial infarcts, attenuated I/R injury, and encouraged cardiac blood flow recovery in I/R rats when compared to quercetin administration alone [178]. By loading SS31, Liu et al. also created a targeted drug delivery system. enveloping them in platelet membranes and releasing peptides into Q-MSNs. They wrapped Q-MSNs in a platelet membrane after loading SS31 peptides into them. The findings showed that the delivery system could effectively stimulate the SS31 peptide's antioxidant property, target the SS31 peptide to the damaged cardiac vascular sites, and reduce myocardial I/Rinjury [179]. Furthermore, in rats with myocardial I/R injury, copper nanoparticle (CuNP) treatment was able to decrease oxidative stress and inflammatory factors, inhibit the glycogen synthase kinase (GSK-3β) pathway, and decrease cardiomyocyte apoptosis [180]. Liposomes

Liposomes are currently the most extensively researched drug delivery system and are acknowledged as effective drug delivery systems for the heart's injury. Liposomes are lipid-and fatty acid-based spherical vesicle systems with a lipophilic bilayer surrounded by two hydrophilic layers. Because liposomes are amphiphilic, they can transport both hydrophilic and lipophilic medicines, making them perfect drug carriers for compounds with varying polarity [181]. Liposomes can extend the duration of a drug's action, promote drug biodistribution, and significantly lower the off-target toxicity of a variety of medications [182].

Although simvastatin (SIM) is now an effective medication for myocardial I/R, its many pharmacologic side effects restrict its clinical usage. The surfactant film-forming hydration approach, on the other hand, may greatly improve the drug's stability, bioavailability, and therapeutic impact against myocardial I/Rinjury when used as delivery vehicles for SIM [183]. ResolvinD1(RvD1)isapotentialsmallmoleculedrug for protection against myocardial I/R damage, whose therapeutic poten- tial is restricted by its small molecular weight and fast enzymatic breakdown in vivo. Weng et al. created a platelet-mimicking,ROS-responsive RvD1 liposome delivery method that inherits the abil- ity of platelets to interact with monocytes, enabling them to reach the

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ISSN 2347-2251 www.iajpb.com
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siteofcardiacinjurybyriddingcirculatingmonocytesafteri ntravenous injection. Large volumes of ROS near the injury site later disintegrate the delivery system, allowing RvD1 to be released quickly. The released RvD1 may significantly reduce myocardial I/R damage by promoting angiogenesis, the removal of dead cardiomyocytes, and the inhibition of mediator synthesis [184]. Gao et al. created a new mitochondria-targeted astaxanthin (AST) liposome, STPP-AST-LIP, tar- geting the mitochondria of cardiomyocytes. STPP-AST-LIP not only decreased ROS generation, but also enhanced cardiomyocyte survival, prevented apoptosis, and improved cardiac function in cardiomyocytes from cardiomyocytes of I/R rats[185]. Extracellularvesicles EVs are nanoscale membrane vesicles made of a lipid bilayer. Various kinds of cells in the body are capable of releasing several subtypesofEVs,suchasexosomes,microvesicles,andapo ptoticbodies [186]. EVs may carry coding and non-coding RNAs such as miRNAs, lncRNAs,andcircRNAs,aswellaslipids,proteins,andsma llmolecule medicines for the treatment of many disorders. Cells in vivo can package different biomolecules into EVs through an endogenous sorting mech- anism and release them after combinatorial molding, which are subse- quently internalized by the target receptor cells, leading to the transfer ofmRNAsandmiRNAs,andconsequentlytotheproductio norsilencing of the corresponding target proteins [187]. EVs are a natural medication delivery vehicle that has many of the characteristics of an excellent carrier system, which protects the payload from deterioration while it is in circulation. Additionally, EVs have outstanding biocompatibility, long-term cycling capabilities, and inherent cell-targeting qualities. As a result, EVs have inherent benefits and enormous promise for therapeutic medication delivery [188,189]. Recent research have identified human plasma-derived extracellular vesicles (EVs) as having tremendous promise for fighting I/RI. The efficient in vivo distribution of hEVs is still a significant barrier to their therapeutic use, nevertheless. The platelet membrane-fused hEVs (P-hEVs) bionic delivery system may harness platelets' inherent affinity to target hEVs more precisely and effectively. ciently to the damaged cardiac and vascular areas and collect them appropriately. Three weeks after myocardial I/R damage, P-hEVs reduce cardiac remodeling and dramatically increase the protective effect against myocardial I/RI [190]. Targeting ATG16L1, plasma-derived EVs that transport miR-130a-3p shield I/R-exposed cardiomyocytes from excessive autophagy and inflammation brought on by I/R, therefore reducing tissue damage and cardiac dysfunction [191]. Furthermore, MSC-derived exosomes, or MSC-Exos, may be very effective in reducing myocardial I/R damage. According to recent research, miR-125a-5p is abundant in MSC-Exos. Its modified oligonucleotide, agomir, is administered intramyocardially in both MSC or MSC-Exos and mouse I/R myocardium. It has a major cardioprotective impact by improving cardiac function and preventing unfavorable remodeling. Furthermore, treatment with miR-125a-5pagomir boosted M2 macrophage polarization, stimulated angiogenesis, and inhibited fibroblast activation and proliferation, which reduced inflammation and cardiomyocyte death [192]. 3. Conclusion and Prospects Myocardial injury may result in cell damage throughout the phases of ischemia and reperfusion, which can have a major impact on heart function and perhaps induce myocardial infarction. As a result, clinics urgently need to reduce the severity of injuries and enhance healing benefits. various phases of cardiac I/R damage include various roles for autophagy. Autophagy exerts cardioprotective benefits during the ischemia phase by removing damaged protein aggregates and organelles and giving cardiomyocytes a source of energy. Excessive buildup of autophagosomes, which causes autophagic death of cardiac myocytes and worsens myocardial damage, is caused by excessive elevation of autophagy levels and obstruction of autophagic flow during the perfusion phase. It has been demonstrated that SIRT1 activates the autophagy process. This review outlines some pertinent mechanisms through which SIRT1 controls autophagy alterations during myocardial I/R; however, more research is required to determine the precise regulatory mechanisms. The current small-molecule natural product-based medications that target the SIRT1-autophagy axis for the treatment of myocardial I/Rinjury are also summarized in this review. However, the relevant studies are still in the animal experimentation stage, and some of the models are still only cellular models, which means they cannot accurately replicate the myocardial I/R model. Therefore, in order to elucidate the function of the SIRT1-autophagyaxis in people, further clinical studies must be conducted in the future. We think that focusing on SIRT1, autophagy, and their interactions will probably be a novel approach to treating myocardial I/R damage in the future as the mechanism of SIRT1-autophagy crossover is further investigated. Additionally, miRNAs have a role in the SIRT1-autophagy axis in myocardial I/R damage. In order to improve myocardial I/R injury treatments, relevant miRNA agonists or blockers may be investigated further in the future.

The therapeutic medications included in this review are given out for free, which has some drawbacks. There is an urgent need for a novel method of drug administration to enhance the therapeutic effects of

Indo-American Journal of Pharma and Bio Sciences

ISSN 2347-2251 www.iajpb.com
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medications since water-soluble medicines have limited bioavailability, short half-life, weak selective targeting, and significant toxicity. The introduction of new nano-deliverysystemscanimprovethebioavailabilityofdrugsin vivo,
whichcanlargelyaddressthelimitationsofcurrentdrugs.
In order to find more effective treatment approaches, nanocarriers may be further paired with medications that target the SIRT1-autophagy axis or other targets in the future, in line with the review's main objective. Even though nanomedicines have advanced, there are still a lot of obstacles to overcome before they can be used in clinical settings. First, large-scale manufacturing is hampered by the structural complexity of nanomedicines, which also contributes to their process complexity. To address the drawbacks of traditional nanocarrier synthesis, new fabrication procedures must be developed in the future [193]. Second, the bulk of myocardial I/R patients are old, and the experimental subjects of nanomedicines are presently myocardial I/R animal models, which tend to have greater immunity and repair capacity, which is radically different from that of humans. Therefore, models that are more closely connected to myocardial I/R in the elderly should be tried in the future. Third, before being used in clinical trials, nanocarrier materials need to be thoroughly and methodically examined since they may be hazardous over the long run. In the future, biocompatible and biodegradable materials with individualized rates of breakdown may be explored as drug carriers. Nanomedicines will undoubtedly be a novel approach with significant promise for the future treatment of myocardial I/R, despite the many challenges.

Indo-American Journal of Pharma and Bio Sciences

ISSN 2347-2251 www.iajpb.com
Vol. 22, Issue 1, Jan 2024

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Vol. 22, Issue 1, Jan 2024

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