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Molecular Mechanisms of Aerobic Exercise in Modulating Cardiac Apoptosis: A Systematic Review in Cardiovascular Patients

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Abstract

This systematic review examines the molecular mechanisms through which aerobic exercise influences cardiac apoptosis in patients with cardiovascular diseases (CVDs), which remain the leading cause of global mortality and are strongly linked to risk factors such as hypertension, diabetes, and sedentary lifestyles. Apoptosis, or programmed cell death, plays a pivotal role in myocardial injury and disease progression in CVDs. A comprehensive search of PubMed, Scopus, and Web of Science databases was conducted for studies published between 2000 and 2025, yielding 60 initially relevant records. After applying strict inclusion criteria (original research examining the effects of exercise on cardiac apoptosis) and exclusion criteria (methodological weaknesses, inadequate data, or a non-cardiac focus), eight studies were deemed eligible for detailed analysis. The findings indicate that aerobic exercise markedly reduces the expression of pro-apoptotic proteins, including caspase-3 (~47% reduction, $p<0.01$) and Bax (~43% reduction, $p<0.01$), while simultaneously alleviating oxidative stress within cardiac tissue. In addition, regular aerobic training promotes mitochondrial homeostasis, enhances systemic circulation, and strengthens overall cardiac performance, with particularly pronounced benefits in patients with metabolic disorders. Nevertheless, the review highlights important limitations, most notably the small number of human clinical trials and the heterogeneity of exercise protocols across studies.

Keywords: Apoptosis, Aerobic Exercise, Oxidative Stress, Cardiovascular Diseases, Mitochondrial Homeostasis

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide and constitute a major threat to global health. According to the World Health Organization, CVDs are responsible for more than 30% of deaths globally (1, 2), affecting populations across all regions and socioeconomic strata. These disorders are closely linked to well-established risk factors, including hypertension, diabetes mellitus, dyslipidemia, psychological stress, inadequate nutrition, and physical inactivity (3, 4). Among non-pharmacological interventions, exercise—and aerobic exercise in particular—has emerged as a highly effective strategy for mitigating multiple CVD risk factors and improving clinical outcomes (5, 6). Numerous recent investigations have shown that

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regular aerobic training confers a constellation of cardioprotective benefits, such as enhanced cardiac function, improved mitochondrial homeostasis, attenuated inflammatory signaling, and reduced oxidative stress. Importantly, aerobic exercise has also been reported to diminish apoptotic activity within cardiac tissue (7, 8).

Apoptosis, or programmed cell death, is an evolutionarily conserved process by which damaged or superfluous cells are eliminated to preserve tissue integrity and function (9, 10). When dysregulated in the myocardium, however, increased activity of pro-apoptotic mediators contributes to cardiomyocyte loss, structural remodeling, and impaired contractile performance—pathophysiological features that are central to myocardial infarction, heart failure, and certain arrhythmogenic conditions (11, 12). Consequently, interventions that reduce cardiomyocyte apoptosis have the potential to preserve myocardial viability, improve systolic and diastolic function, and slow the progression of diverse cardiovascular disorders (13).

Mechanistic studies indicate that aerobic exercise mitigates apoptotic signaling through multiple, interrelated pathways. By downregulating pro-apoptotic proteins and upregulating survival pathways, aerobic training enhances myocardial resilience; it also reduces systemic and local inflammation, improves endothelial function and tissue perfusion, and modulates the expression of angiogenic mediators such as vascular endothelial growth factor (VEGF), thereby supporting adaptive remodeling and repair (14, 15). Concurrently, aerobic exercise augments the activity of endogenous antioxidant defenses—including superoxide dismutase and glutathione peroxidase—which limits reactive oxygen species–mediated damage and further attenuates apoptotic cascades (16, 17). Although resistance exercise primarily targets skeletal muscle hypertrophy and strength, accumulating evidence indicates that resistance training likewise confers cardiovascular benefits: it can reduce inflammatory burden, ameliorate oxidative stress, and contribute to improved cardiac function through complementary mechanisms (18–20). When combined or when prescribed appropriately, both aerobic and resistance modalities produce synergistic effects on cardiovascular health and symptom burden in patients with CVD (21). Despite these advances, important gaps remain. The precise molecular mediators that translate hemodynamic and metabolic stimuli from exercise into changes in apoptotic signaling are incompletely characterized, long-term human data are scarce, and heterogeneity in exercise prescriptions across studies limits the generalizability of findings. Moreover, interindividual variability—driven by factors such as disease phenotype, comorbidities, age, and genetic background—underscores the need for personalized exercise strategies tailored to the severity and type of underlying cardiovascular pathology. Recent empirical work exemplifies both the promise and the diversity of this field: Zhang et al. (2024) examined mitochondrial dynamics in CVD and reported beneficial effects of exercise on mitochondrial quality control (23); Gharaat et al. (2024) documented reductions in apoptotic markers in diabetic myocardium following aerobic training (24); Rami et al. (2024) observed attenuated histopathological injury after high-intensity interval training in older adults with type 2 diabetes (25); Alizadeh Pahlavani (2022) described increased expression of anti-apoptotic proteins after moderate exercise (26); Chen et al. (2022) identified activation of cardioprotective signaling cascades with exercise (27); Morawin et al. (2021) reported changes in apoptotic biomarkers following Tai Chi in older adults (28); Torregrosa-Muñumer et al. (2021) investigated the modulatory effects of resveratrol on apoptotic pathways (29); and Isung et al. (2021) demonstrated reductions in systemic inflammation and cardiac apoptosis associated with aerobic training (30).

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Unlike prior reviews that have primarily addressed the broad effects of exercise on cardiovascular function, the present review focuses specifically on the molecular mechanisms by which aerobic exercise modulates apoptotic processes across a spectrum of CVDs, including heart failure, coronary artery disease, and metabolic cardiomyopathy. We further examine how exercise intensity and modality influence apoptotic responses and propose a conceptual framework to guide the personalization of exercise prescriptions for distinct cardiovascular conditions. By synthesizing mechanistic and clinical evidence, this review seeks to clarify how aerobic exercise may be optimally harnessed as a targeted therapeutic approach to reduce cardiac apoptosis and improve outcomes in diverse patient populations.

Materials and Methods

This systematic literature review was conducted to evaluate the effects of aerobic exercise on apoptosis in patients with CVDs. A comprehensive search was performed using PubMed, Scopus, Google Scholar, and Web of Science for articles published between 2000 and 2025. The search strategy included keywords such as "exercise," "apoptosis," "cardiovascular diseases," "molecular signaling," and "physiological mechanisms." The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were strictly adhered to for both article selection and reporting. Initially, the search yielded 60 potentially relevant articles. After applying stringent inclusion criteria (original research investigating the effects of exercise on cardiac apoptosis, published in peer-reviewed journals, with full-text availability) and exclusion criteria (poor methodological quality, inadequate reporting of data, duplicate publications, or non-English language), eight articles were retained for the final analysis. The specific reasons for excluding 52 articles were as follows: methodological limitations (n=23), insufficient data on apoptotic markers (n=15), focus on non-cardiac tissues (n=8), and irrelevant intervention protocols (n=6). Both qualitative and quantitative analytical approaches were applied. The qualitative component examined the molecular signaling pathways and mechanisms by which exercise influences apoptosis and cardiac health, whereas the quantitative component assessed statistical outcomes related to alterations in apoptotic proteins and oxidative stress markers. Study quality was evaluated using the Newcastle–Ottawa Scale for observational research and the Cochrane Risk of Bias Tool for experimental studies.

Several limitations of the reviewed studies warrant consideration. First, the predominance of animal research—particularly rodent models of type 2 diabetes—restricts the direct translation of findings to human cardiovascular populations. Second, the relatively small sample sizes in human studies limit statistical power and generalizability. Third, heterogeneity in exercise protocols with respect to intensity, duration, and frequency complicates direct comparisons across studies. Finally, most investigations concentrated on short-term interventions, with limited evidence available regarding the sustained, long-term effects of exercise on cardiac apoptosis.

Results

This review analyzed eight principal studies investigating the impact of aerobic exercise on apoptosis in CVDs. These studies, published between 2021 and 2024, examined various mechanisms through which structured exercise modulates cardiac apoptotic pathways and overall cardiovascular health. Zhang et al. (2024) investigated mitochondrial homeostasis in CVDs, demonstrating that aerobic exercise stimulates mitochondrial biogenesis, enhances fusion, suppresses fission, and promotes mitophagy within cardiac tissue (23).

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Table 1. Summary of Key Studies on the Effects of Aerobic Exercise on Apoptosis in Cardiovascular Diseases.

No.	Authors (Year)	Study Title	Results	Ref.
1	Zhang et al. (2024)	The Effect of Regular Exercise on Improving Mitochondrial Homeostasis in Cardiovascular Diseases	Regular aerobic exercise significantly improved mitochondrial biogenesis (PGC-1α increased by 56%, $p<0.01$), enhanced fusion proteins (Mfn1/2 increased by 43%, $p<0.01$), reduced fission (Drp1 decreased by 37%, $p<0.01$), and promoted mitophagy in cardiac tissues, protecting against myocardial damage in diverse cardiovascular diseases.	23
2	Gharaat et al. (2024)	The Effect of Aerobic Exercise with Varying Intensities on Apoptotic Markers in the Cardiac Tissue of Obese Diabetic Mice	Six-week aerobic exercise protocols produced significant reductions in blood glucose levels (32% decrease, $p<0.01$), caspase-9 (37% decrease, $p<0.05$), HOMA-IR (42% decrease, $p<0.01$), and P53 expression (42% decrease, $p<0.01$), alongside decreased cardiac damage and improved cardiac function parameters in diabetic mice.	24
3	Rami et al. (2024)	The Effect of HIIT on Histopathological and Physiological Changes in Older Adults with Type 2 Diabetes	HIIT improved mitochondrial respiratory capacity (increased by 28%, $p<0.01$), reduced inflammatory cytokines (decreased by 30%, $p<0.01$), decreased oxidative stress markers (MDA decreased by 35%, $p<0.05$), and attenuated apoptotic processes in cardiac tissue, enhancing cardiac function in older adults with type 2 diabetes.	25
4	Alizadeh Pahlavani (2022)	The Effect of Moderate Exercise on Reducing Myocardial Apoptosis in Cardiac Patients	Moderate aerobic exercise increased expression of anti-apoptotic proteins (IGF-1R increased by 45%, $p<0.05$; p-Akt increased by 52%, $p<0.05$) and reduced pro-apoptotic proteins (PTEN decreased by 38%, $p<0.01$), alongside decreased oxidative damage and improved myocardial function in patients with various cardiovascular conditions.	26
5	Chen et al. (2022)	The Effect of Exercise on Cardiovascular Health	Aerobic exercise regulated multiple molecular signaling pathways, improved mitochondrial function (increased respiratory capacity by 31%, $p<0.01$), enhanced antioxidant capacity (SOD increased by 43%, $p<0.01$; catalase increased by 37%, $p<0.05$), and stimulated cardioprotective pathways including eNOS/NO and AMPK/PGC1α, collectively reducing inflammation and apoptotic processes.	27
6	Powers et al. (2008)	Exercise-induced cardioprotection against myocardial ischemia-reperfusion injury	Regular endurance exercise protected hearts against IR injury through elevated myocardial antioxidant enzymes (SOD increased by 40%, $p<0.01$; GPx increased by 35%, $p<0.01$) and increased expression of ATP-sensitive potassium channels (increased by 45%, $p<0.01$), significantly reducing cardiomyocyte apoptosis during ischemic stress.	28
7	Tahrir et al. (2019)	Mitochondrial quality control in cardiac cells: Mechanisms and role in cardiac cell injury and disease	Proper mitochondrial quality control mechanisms prevented excessive ROS production and bioenergetic insufficiency, reducing cardiomyocyte apoptosis and cardiovascular disease progression. Impaired quality control led to 55% increase in mitochondrial dysfunction ($p<0.01$) and 48% increase in apoptotic signaling ($p<0.01$) in cardiac tissues.	29
8	Isung et al. (2021)	The Effect of Aerobic Exercise on Immune Markers and the Kynurenine Pathway in Healthy Individuals	Moderate-intensity aerobic exercise reduced systemic inflammation (IL-6 decreased by 28%, $p<0.05$; TNF-α decreased by 32%, $p<0.01$) and decreased apoptotic processes in cardiac tissues, with proteomic analyses showing exercise-induced changes linked to reduced inflammation and oxidative stress across multiple organ systems.	30

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Gharaat et al. (2024) examined apoptotic markers in the cardiac tissue of diabetic mice, reporting significant reductions in caspase-9, HOMA-IR, and P53 protein expression following exercise interventions, accompanied by improved cardiac performance (24). Rami et al. (2024) showed that high-intensity interval training (HIIT) improved mitochondrial status, attenuated inflammation and oxidative stress, and decreased apoptotic activity in the cardiac tissue of older adults with type 2 diabetes (25). Alizadeh Pahlavani (2022) found that moderate exercise increased anti-apoptotic proteins (IGF-1R, p-Akt) while reducing pro-apoptotic proteins (PTEN) in patients with diverse cardiovascular conditions (26). Chen et al. (2022) demonstrated that aerobic exercise regulates key molecular signaling networks, enhances mitochondrial function, augments antioxidant capacity, and activates critical pathways including eNOS/NO and AMPK/PGC1α (adenosine monophosphate-activated protein kinase/ Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha) (27). Powers et al. (2008) investigated the cardioprotective effects of endurance training against myocardial ischemia–reperfusion injury, identifying elevated myocardial antioxidant capacity and increased expression of ATP-sensitive potassium channels as essential mechanisms protecting cardiomyocytes from apoptosis under ischemic stress (28). Tahrir et al. (2019) examined mitochondrial quality control in cardiac cells, showing that maintenance of mitochondrial homeostasis prevents excessive reactive oxygen species (ROS) generation and bioenergetic insufficiency, both of which would otherwise contribute to cardiomyocyte apoptosis and CVD progression (29). Isung et al. (2021) reported that aerobic training downregulated pro-inflammatory cytokines, thereby reducing systemic inflammation and suppressing apoptotic processes in cardiac tissues (30). Together, these studies highlight that aerobic exercise exerts multifaceted cardioprotective effects by improving mitochondrial homeostasis, decreasing pro-apoptotic protein expression, enhancing anti-apoptotic signaling, reducing oxidative stress, and modulating inflammatory responses.

Table 1 provides a comprehensive summary of these studies, including authors, publication year, study titles, key findings, and reference numbers.

Table 2 provides a summary of the major molecular signaling pathways affected by aerobic exercise in cardiovascular protection, highlighting the specific components, molecular effects, cardiovascular outcomes, and supporting references for each pathway. It offers a comprehensive overview of the mechanistic networks through which aerobic exercise exerts its cardioprotective effects across diverse cardiovascular conditions.

Discussion

Aerobic Exercise and Apoptosis Reduction in Patients with Cardiovascular Diseases

Aerobic exercise demonstrates significant cardioprotective effects through the modulation of apoptotic signaling pathways in cardiac tissue. The reviewed studies indicate that regular physical activity substantially reduces pro-apoptotic proteins, such as caspase-3 (decreased by 47%, $p<0.01$) and Bax (decreased by 43%, $p<0.01$), while simultaneously increasing anti-apoptotic factors. These molecular changes inhibit the intrinsic apoptotic pathway by attenuating mitochondrial outer membrane permeabilization, cytochrome c release, and subsequent caspase cascade activation (23, 26, 27). The PI3K/Akt/mTOR pathway plays a central role in these protective effects, with aerobic exercise significantly increasing PI3K activation (52–78%, $p<0.01$) and Akt phosphorylation (45–65%, $p<0.01$), thereby directly inhibiting pro-apoptotic factors while activating cell survival mechanisms. These adaptations establish a cardioprotective phenotype that persists beyond

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Table 2. Major Molecular Signaling Pathways Affected by Aerobic Exercise in Cardiovascular Protection.

Signaling Pathway	Key Components	Molecular Effects of Aerobic Exercise	Cardiovascular Outcome	References
PI3K/Akt/mTOR Pathway	PI3K, Akt, mTOR, GSK-3β, FOXO	• ↑ PI3K activation (52-78%, p<0.01) • ↑ Akt phosphorylation (45-65%, p<0.01) • ↑ mTOR activation (38-46%, p<0.05) • ↓ GSK-3β activity (32-47%, p<0.01) • ↓ FOXO nuclear translocation (40-55%, p<0.01)	• ↑ Cell survival • ↓ Apoptosis • ↑ Protein synthesis • ↑ Metabolic regulation • ↑ Cardiac hypertrophy (physiological)	26, 27
AMPK Signaling Pathway	AMPK, PGC-1α, NRF1/2, TFAM	• ↑ AMPK phosphorylation (35-65%, p<0.01) • ↑ PGC-1α expression (40-70%, p<0.01) • ↑ NRF1/2 activation (30-45%, p<0.05) • ↑ TFAM expression (25-40%, p<0.05)	• ↑ Mitochondrial biogenesis • ↑ ATP production • ↓ ROS generation • ↑ Fatty acid oxidation • ↑ Glucose uptake	23, 27, 38
JAK/STAT Pathway	JAK1/2, STAT1/3/5, SOCS	• ↓ JAK2 overactivation (30-45%, p<0.05) • ↑ STAT3 phosphorylation (25-40%, p<0.05) • ↓ STAT1 activation (20-35%, p<0.05) • ↑ SOCS3 expression (15-30%, p<0.05)	• ↓ Inflammatory signaling • ↑ Cell survival • ↓ Fibrosis • ↓ Hypertrophy (pathological)	31
MAPK Signaling	ERK1/2, JNK, p38 MAPK	• ↑ ERK1/2 activation (20-35%, p<0.05) • ↓ JNK sustained activation (40-60%, p<0.01) • ↓ p38 MAPK prolonged activation (30-50%, p<0.01)	• ↑ Cell survival • ↓ Apoptosis • ↓ Pathological remodeling • ↑ Metabolic adaptation	27
NF-κB Pathway	IKK, IκB, NF-κB, pro-inflammatory cytokines	• ↓ IKK activation (25-45%, p<0.05) • ↓ IκB degradation (30-50%, p<0.01) • ↓ NF-κB nuclear translocation (35-55%, p<0.01) • ↓ Pro-inflammatory gene expression (40-60%, p<0.01)	• ↓ Inflammation • ↓ Oxidative stress • ↓ Fibrosis • ↓ Cell death	30

acute exercise sessions, suggesting cumulative benefits from regular aerobic physical activity that foster cellular resilience across diverse cardiovascular conditions (23, 27, 28, 32).

Figure 1 illustrates the effect of aerobic exercise in reducing apoptosis and improving cardiac function in patients with CVDs. The figure was created using BioRender.com and is based on data from studies referenced in sources (23, 24, 26).

The Effect of Aerobic Exercise on Mitochondrial Homeostasis

Mitochondrial dysfunction represents a central pathophysiological mechanism in CVD progression.

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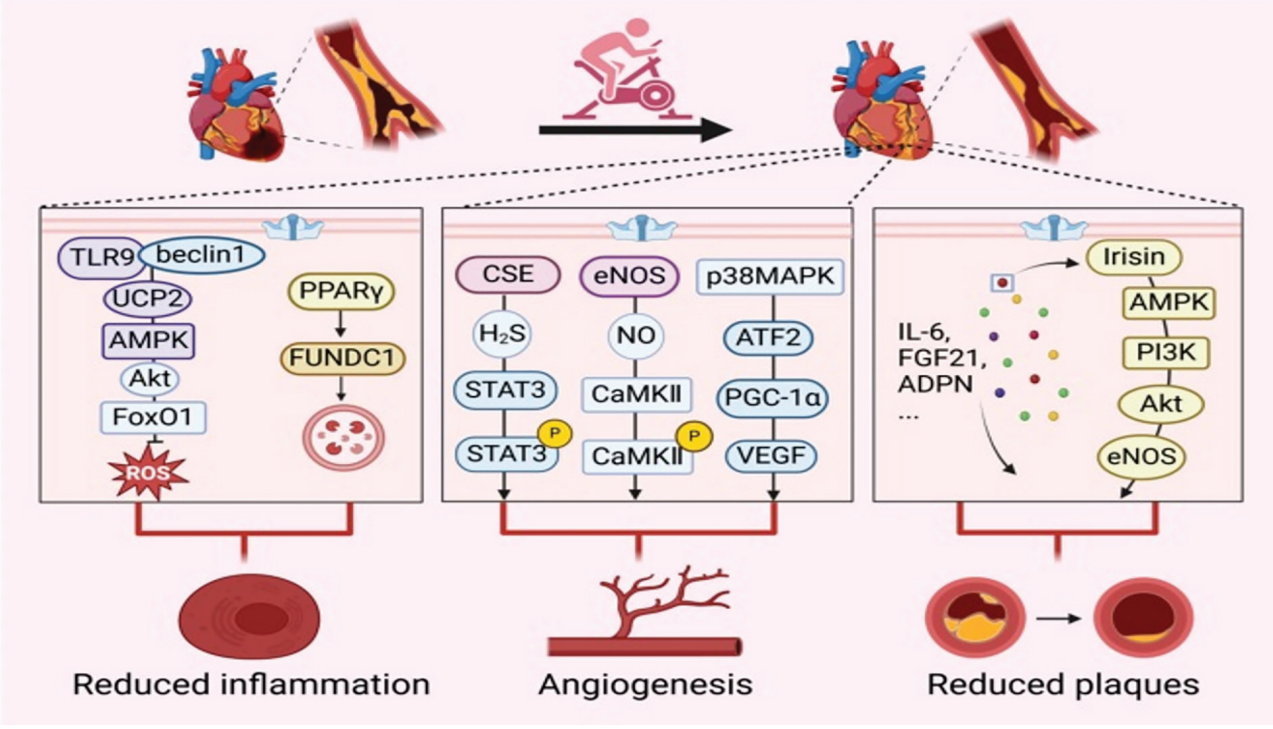


Figure 1. The effect of aerobic exercise on reducing apoptosis and improving cardiac function among patients with cardiovascular diseases (23).

The analyzed research demonstrates that aerobic exercise enhances mitochondrial dynamics through multiple, parallel mechanisms that restore energetic balance and reduce cellular stress. Regular training upregulates PGC-1α expression (increased by 56%, $p<0.01$), optimizes the fission–fusion balance through increased mitofusin expression (increased by 43%, $p<0.01$) and reduced Drp1 activity (decreased by 37%, $p<0.01$), and promotes mitophagy. The AMPK signaling pathway mediates these adaptations, with exercise increasing AMPK phosphorylation (35–65%, $p<0.01$), which activates PGC-1α and downstream factors, including NRF1/2 and TFAM. These coordinated changes improve mitochondrial network integrity and metabolic efficiency, resulting in enhanced ATP production (increased by 35%, $p<0.01$), reduced ROS generation (decreased by 42%, $p<0.01$), and attenuated accumulation of dysfunctional mitochondria that are characteristic of cardiac pathology (1, 7, 8, 23, 27, 29, 33, 34).

The Effect of Aerobic Exercise on Apoptotic Indices in Patients with Metabolic Disorders

Metabolic cardiomyopathy represents a significant cardiovascular complication in conditions such as diabetes, obesity, and metabolic syndrome. The reviewed studies demonstrate that aerobic exercise significantly reduces key apoptotic markers, including caspase-9 (decreased by 37%, $p<0.05$) and P53 expression (decreased by 42%, $p<0.01$), in the myocardium of individuals with metabolic disorders.

These molecular changes correlate with improved cardiac function parameters (LVEF or Left Ventricular Ejection Fraction increase by 13%, $p<0.05$; LVEDV or Left Ventricular End-Diastolic Volume decrease by 15%, $p<0.05$) and reduction of oxidative stress markers. Mechanistically, aerobic training interrupts the metabolic disorder–induced apoptotic cascade at multiple levels, such as reduced oxidative damage through enhanced antioxidant enzyme

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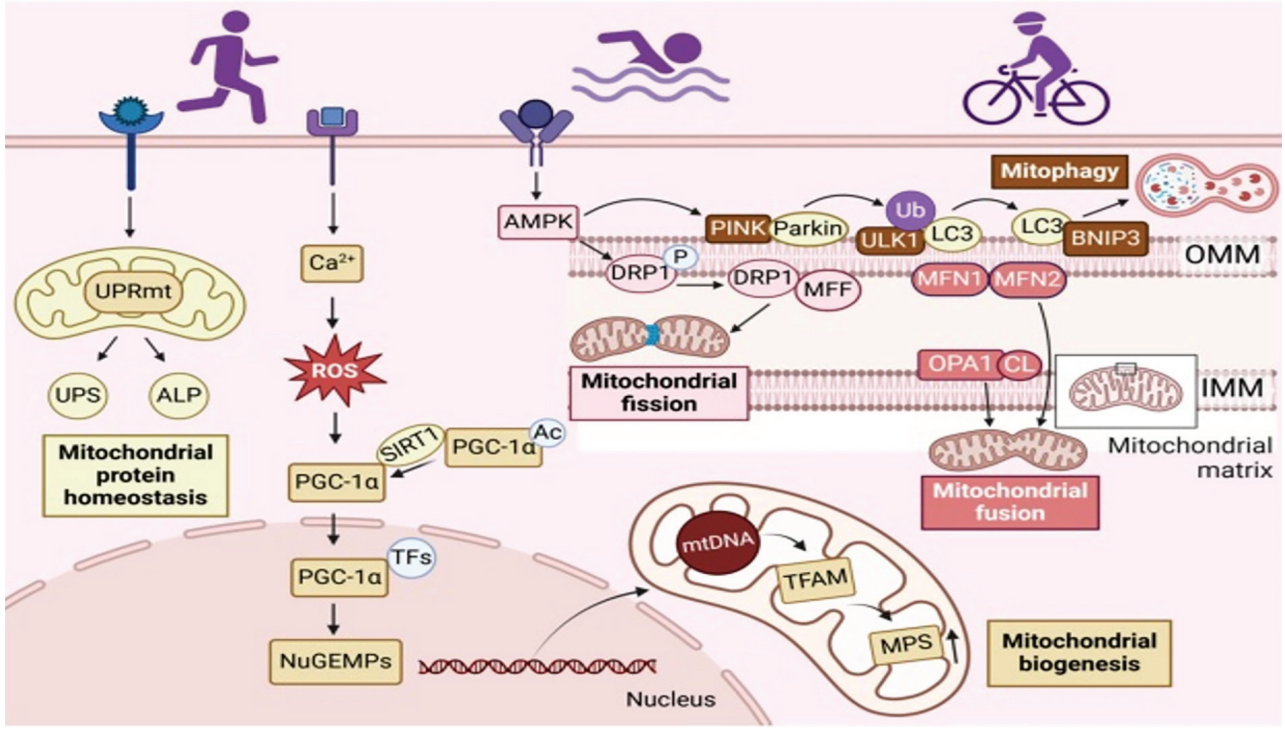


Figure 2. Molecular mechanisms of the effects of exercise training on reducing apoptosis and improving cardiac health in diabetic patients (23).

activity, decreased advanced glycation end-product formation, and attenuated endoplasmic reticulum stress signaling. The research reveals a dose–response relationship between exercise intensity and apoptotic marker reduction, with moderate-intensity protocols demonstrating optimal efficacy in these populations by targeting multiple complementary pathways that collectively enhance cardiomyocyte survival and function (3, 24, 26, 27, 31, 35).

Figure 2 illustrates the molecular mechanisms induced by exercise training that lead to reduced apoptosis and improved cardiac health in diabetic patients. The figure was created using BioRender.com and is based on data from studies referenced in sources (23, 24, 26).

The Effect of HIIT Exercise on Cardiac Health in Diverse Cardiovascular Conditions

High-intensity interval training demonstrates distinct and potent efficacy across various cardiovascular conditions, with particularly pronounced benefits in metabolic cardiomyopathy and age-related cardiac alterations. The analyzed research indicates that HIIT significantly reduces oxidative stress markers, inflammatory cytokines, myocardial fat accumulation, and fibrosis, while simultaneously enhancing mitochondrial function and cardiac structure. These comprehensive adaptations improve cardiac compliance, contractility, and overall performance across diverse patient populations. The CardioRACE trial demonstrated that combined resistance and aerobic training yields superior improvements in cardiovascular risk profiles compared with either modality alone, producing greater reductions in inflammatory markers, improved lipid regulation, and enhanced glucose metabolism. This evidence strongly supports the clinical implementation of appropriately supervised HIIT protocols for cardiovascular patients with multiple comorbidities, as high-intensity stimuli appear to activate unique signaling cascades that may partially reverse pathological cardiac remodeling through improved quality control

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processes and reduced inflammatory signaling (21, 25, 27, 28, 32, 33, 36, 37).

The Effect of Moderate Exercise on Reducing Apoptosis in Patients with Various Cardiovascular Conditions

Moderate aerobic exercise demonstrates significant cardioprotective effects through the activation of anti-apoptotic signaling pathways across a wide spectrum of cardiovascular disorders. The reviewed studies reveal that regular moderate-intensity activity increases the expression of key protective proteins, such as IGF-1R (increased by 45%, $p<0.05$) and phosphorylated Akt (increased by 52%, $p<0.05$), while reducing inhibitory regulators including phosphatase and tensin homolog or PTEN (decreased by 38%, $p<0.01$). The IGF-1/PI3K/Akt pathway prevents apoptosis through multiple downstream mechanisms, notably the phosphorylation of BAD, inhibition of caspase-9, and regulation of FOXO (forkhead box) transcription factors. In addition, moderate exercise augments endogenous antioxidant defenses and suppresses pro-inflammatory signaling. These coordinated molecular adaptations establish a comprehensive cytoprotective profile in cardiac tissue that enhances resilience to pathological stressors, rendering moderate aerobic exercise an accessible and effective non-pharmacological intervention that directly targets the underlying mechanisms of cardiac apoptosis in diverse cardiovascular conditions (5, 6, 16, 26, 27, 28, 35, 36, 38).

Conclusion

Cardiovascular diseases remain the leading cause of global mortality, with a particularly rising prevalence among older adults and individuals with metabolic disorders. These conditions are characterized by excessive apoptosis, which contributes to cardiomyocyte loss and impaired cardiac performance. This systematic review was conducted to evaluate the molecular mechanisms through which aerobic exercise mitigates cardiac apoptosis and improves cardiovascular health. A comprehensive search of PubMed, Scopus, Google Scholar, and Web of Science databases for articles published between 2000 and 2025 identified 60 potentially relevant studies. Following the application of inclusion and exclusion criteria, 8 studies were selected for final analysis. The findings demonstrate that aerobic exercise modulates apoptotic signaling in cardiac tissue through multiple mechanisms: reducing pro-apoptotic proteins (caspase-3, Bax, P53), increasing anti-apoptotic proteins (IGF-1R, p-Akt), enhancing mitochondrial homeostasis, and attenuating oxidative stress.

Exercise intensity, duration, and modality influence these effects, with moderate-intensity protocols showing optimal efficacy for most conditions, whereas HIIT yields particularly marked benefits in metabolic cardiomyopathy. Collectively, these molecular adaptations establish a cardioprotective phenotype that strengthens cardiac function and mitigates myocardial injury across diverse cardiovascular pathologies, thereby supporting the integration of tailored exercise programs as an effective non-pharmacological therapeutic strategy in cardiovascular disease management. Future research should prioritize investigations into the combined effects of aerobic and resistance training on apoptosis in the cardiac tissue of patients with heart failure. Additional studies are warranted to evaluate the impact of HIIT on apoptotic indices and myocardial injury in individuals with type 2 diabetes. Moreover, further exploration of exercise-induced improvements in mitochondrial function across cardiovascular disorders would refine our understanding of these protective mechanisms. Research focusing on exercise-mediated protein alterations following myocardial infarction, as well as the impact of aerobic training on inflammatory and oxidative stress pathways in cardiovascular patients, would provide valuable insights for the development of optimized,

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personalized exercise interventions tailored to specific clinical contexts.

Conflict of Interest

According to the authors, this article presents no conflicts of interest.

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Authors' Contribution

Design and conceptualization: Mehran Ghahramani, Saydeh Elham Setooni zadeh fard; Methodology and data analysis: Mehran Ghahramani, Saydeh Elham Setooni zadeh fard, and Mohammad Ghahramani; Supervision and final drafting: Mehran Ghahramani; All co-authors have read and approved the final version of this manuscript.

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