

Original Article



High-Intensity Interval Training Plus Resveratrol: A Synergistic Strategy to Rejuvenate the Aging Heart via VEGF/FSTL1/DIP2 Signaling

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Abstract

Introduction: Aging impairs cardiac angiogenesis via downregulated molecular pathways. While exercise and resveratrol each exhibit pro-angiogenic potential, their combined effect on vascular endothelial growth factor (VEGF), follistatin-like 1 (FSTL1), and disco-interacting protein 2 homolog A (DIP2A) in the aged heart remains unclear. This study investigated eight-week high-intensity interval training (HIIT) and resveratrol on these proteins in aged rat hearts.

Methods: Twenty-four 15-month-old male rats were randomly divided into sedentary control, HIIT only, resveratrol only, and HIIT + resveratrol groups (n=6 per). The HIIT protocol involved eight weeks of progressive treadmill running, while resveratrol (15 mg/kg/day) was orally administered throughout the same period. Cardiac tissue was harvested 24 hours post-intervention, and protein expression levels were analyzed via Western blotting.

Results: One-way ANOVA revealed significant differences among groups for all proteins ($P=0.001$). Post-hoc Tukey's HSD tests demonstrated that the exercise+resveratrol group had the highest levels of VEGF, FSTL1, and DIP2A, significantly exceeding those of all other groups ($P<0.001$). Exercise alone substantially increased all markers compared with the control and resveratrol groups ($P<0.001$). Critically, resveratrol alone did not differ from control for any protein (VEGF: $P=0.99$; FSTL1: $P=0.47$; DIP2A: $P=0.99$), indicating that supplementation was ineffective in the absence of exercise. The combined group's superiority over exercise alone confirmed that resveratrol synergistically potentiated the exercise-induced upregulation of VEGF, FSTL1, and DIP2 in the aged heart.

Conclusion: Exercise training was the strongest stimulus for VEGF, FSTL1, and DIP2A. Resveratrol alone had minimal effect, but when combined, they synergistically markedly maximized cardiovascular health benefits.

Keywords: High-intensity interval training, Resveratrol, Angiogenesis

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Introduction

Preclinical and clinical studies indicate that aging is one of the main causes of endothelial dysfunction, which is an early feature of atherosclerotic vascular diseases and significantly contributes to impaired microvascular perfusion (1). In this regard, some studies have shown that the mechanisms contributing to aging-related angiogenesis impairments are likely multifaceted (2).

A follistatin-dependent pathway is one of the mechanisms affecting vascular endothelial growth factor (VEGF) and angiogenesis. Follistatin-like 1 (FSTL1) protein, also known as follistatin-related protein or TGF β -activated clone 36, is an extracellular glycoprotein that belongs to a family of secreted cysteine-rich acidic proteins (3). Additionally, disco-interacting protein 2 homolog A (DIP2A), a cell surface receptor for FSTL1, combines with FSTL1 and is involved in vascular and immune response regulation (3). Moreover, FSTL1 positively correlates with platelet endothelial cell adhesion molecule-1 in patients with heart failure, suggesting it may improve angiogenesis (4). Shimano et al reported

that cardiac FSTL1 activates adenosine monophosphate (AMP)-activated protein kinase (AMPK) and nitric oxide synthase 3 (NOS3) in mice, leading to NO production, a critical mediator in myocardial angiogenesis (5). Overall, data to date indicate that FSTL1 promotes angiogenesis, with FSTL1 binding to the DIP2A receptor to regulate angiogenesis (6).

According to some studies, physical activity can stimulate the production of the FSTL1 protein, which is synthesized in skeletal muscle tissues. This protein has shown its ability to increase endothelial cell proliferation and facilitate tube formation under in vitro conditions. Furthermore, it improves angiogenesis in cardiac tissues and provides protection after myocardial infarction (MI) and cardiac dysfunction (7). Xi et al examined the effect of dynamic resistance exercises and found that they increase the level of the FSTL1 protein produced by skeletal muscle tissues. This increase in protein level influences cardiac angiogenesis and, through the DIP2A-mothers against decapentaplegic homolog 2/3 (Smad2/3) pathways, helps stimulate cardiac responses against MI in mouse models

(6). Likewise, Inoue et al observed that aerobic exercise-induced FSTL1 secretion in slow-twitch fiber-rich muscles may be associated with reduced arterial stiffness through arterial NO production in obese mice (8). To the best of our knowledge, there is no precise and specific information regarding the effect of physical activities on cardiac FSTL1 levels in elderly individuals and its impact on the angiogenesis process.

Meanwhile, the use of dietary supplements is also of great importance. Resveratrol is one such supplement, which can act as an effective and safe agent in preventing age-related diseases. This compound has the potential to reduce atherosclerosis and enhance cardiovascular function. Ling et al and Zhu et al demonstrated that resveratrol activates endogenous cardiac stem cells and improves myocardial remodeling after acute MI (2, 9). Similarly, Feng et al concluded that resveratrol protects against isoproterenol-induced MI in rats via the VEGF-B/AMPK/endothelial NOS/NO signaling pathway (10). Regarding FSTL1 and DIP2A, no results were found on the effects of resveratrol. However, results by Zou et al revealed that resveratrol reduces pressure overload-induced cardiac fibrosis and diastolic dysfunction through the phosphatase and tensin homolog/protein kinase B (AKT)/Smad2/3 and nuclear factor kappa-light-chain-enhancer of activated B cells signaling pathways (11). Additionally, Yu et al reported that resveratrol activates phosphoinositide 3-kinase/AKT in order to reduce cardiomyocyte apoptosis and mitochondrial oxidative damage caused by myocardial ischemia/reperfusion injury (12). It seems that a combination of exercise and resveratrol intake leads to superior results on factors affecting angiogenesis in aged samples. Therefore, this study aims to investigate the effect of eight weeks of high-intensity interval (HIIT) training and resveratrol consumption on VEGF, FSTL1, and DIP2A levels in the heart tissue of aged rats.

Materials and Methods

Experimental Animals

Overall, 24 male Wistar rats, aged approximately 15 months and weighing between 280–320 g, were recruited as the experimental population. Upon transfer to the laboratory, the animals were acclimated for one week under controlled environmental conditions in transparent polycarbonate cages, housing three rats per cage. In addition, standard laboratory conditions were maintained during acclimatization, including an ambient temperature of $23 \pm 2^\circ\text{C}$, relative humidity of 45–55%, and a 12:12 hour light-dark cycle. It should be noted that animals had ad libitum access to standard pelleted chow and water throughout the experimental period.

Experimental Groups

Following the acclimatization phase, rats were randomly assigned to four groups ($n=6$ per group), including sedentary aged control (no intervention), aged rats undergoing HIIT, aged rats receiving resveratrol

supplementation, and aged rats receiving both HIIT and resveratrol concurrently.

Randomization and Blinding

Following one week of acclimatization, the rats were randomly allocated to four groups using a computer-generated random number sequence (block randomization with a block size of 4 to ensure balanced group sizes). Further, the allocation sequence was generated by an independent researcher not involved in the subsequent experimental procedures. To minimize bias, all outcome assessments, including tissue harvesting, protein extraction, Western blotting, and densitometric quantification, were performed by an investigator blinded to the group assignments. Furthermore, sample tubes and membranes were labeled with codes that concealed the treatment identity until all analyses were completed. Given the nature of the interventions, full blinding of the personnel administering the exercise training and oral gavage was not feasible; however, these individuals were not involved in the final biochemical analyses or data interpretation.

High-Intensity Interval Training Protocol

A structured HIIT regimen was implemented to investigate the physiological adaptations induced by exercise. The training protocol included ten cycles of 4-minute high-speed running, followed by 2-minute active recovery (low-speed running). The treadmill speed was progressively increased from 18 m/min in the first week to 30 m/min by the eighth week. Moreover, training was conducted six times per week for eight weeks using a motorized treadmill specifically designed for rodents. Each session began with a 7-minute warm-up and finished with a 5-minute cool-down at reduced speed. Additionally, animals underwent a familiarization phase one week prior to the main training period. The incremental speed adjustments were maintained weekly, reaching a steady plateau during the final two weeks (13). The training model was also adapted based on the protocol described by Hofstad et al, which has been validated to elicit significant metabolic and cardiovascular benefits in rodent models (14).

Resveratrol Supplementation

Resveratrol ($\geq 98\%$ purity; Sigma-Aldrich, USA) was orally administered via gavage at a dosage of 15 mg/kg body weight per day. The compound was dissolved in distilled water containing 0.5% carboxymethyl cellulose as a vehicle. To ensure stability, fresh solutions were prepared every three days, protected from light, and stored at 4°C . Prior to administration, the solution was sterilized by filtration through a $0.22 \mu\text{m}$ membrane filter, avoiding potential thermal degradation associated with autoclaving. The concentration and purity of trans-resveratrol in the prepared solution were confirmed by high-performance liquid chromatography-ultraviolet analysis at baseline and after 72 hours of storage, showing

no detectable isomerization to the cis-form or formation of degradation products. Supplementation continued for eight weeks. To minimize circadian variation, animals in the resveratrol groups (groups 3 and 4) received the prepared solution at a fixed time daily (10: 00 AM), while the control groups (groups 1 and 2) received an equivalent volume of the vehicle only (15).

Tissue Collection and Protein Analysis

Twenty-four hours after the final training session and supplement administration, all animals underwent overnight fasting (12 hours) and were then anesthetized using an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). The heart was aseptically excised upon the confirmation of deep anesthesia based on the absence of spinal reflexes. Next, the left ventricle was immediately cooled on ice, snap-frozen in liquid nitrogen within 2 minutes, and stored at -80°C for further analyses. It should be noted that all subsequent biochemical analyses and Western blot quantifications were performed by an investigator blinded to the experimental group allocation. Total protein extraction from cardiac tissue was conducted using radioimmunoprecipitation assay lysis buffer supplemented with protease and phosphatase inhibitors. Subsequently, homogenized samples were centrifuged, and the supernatant was collected. Protein concentrations were also determined via the bicinchoninic acid assay. Furthermore, equal amounts of protein (20–30 μg) were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes using a wet-transfer system. Then, membranes were blocked and incubated with primary and horseradish peroxidase-conjugated secondary antibodies, followed by chemiluminescence detection using an enhanced chemiluminescence kit. Likewise, signal bands were visualized and quantified using a Chemidoc imaging system. Protein band intensities were also normalized to β -actin as a loading control. After the chemiluminescence detection of the target proteins, membranes were stripped and reprobed with an anti- β -actin primary antibody (1:5000; Abcam, ab8227) and corresponding horseradish peroxidase-conjugated secondary antibody.

Laboratory Equipment and Reagents

The study employed high-precision equipment, including homogenizer (IKA T10 basic, Germany), refrigerated centrifuge (Thermo Scientific Heraeus, USA), analytical balance (Sartorius, Germany), and electrophoresis unit (Mini-PROTEAN, Bio-Rad, USA). Other equipment encompassed power supply (Bio-Rad PowerPac Basic),

wet transfer system with integrated cooling, and ChemiDoc imaging system (Bio-Rad ChemiDoc MP).

Additional materials included 37°C incubators, roller shakers, micropipettes, polyvinylidene fluoride membranes (Millipore), and ready-to-use buffers (radioimmunoprecipitation assay, TBST, Laemmli). Specific antibodies used for Western blotting were against VEGF (MyBioSource), FSTL1 (Cell Signaling Technology, Danvers, MA USA), and DIP2A (Abcam). All necessary interventions involving rodents, including exercise and supplementation, were performed using appropriate laboratory-grade treadmills and delivery instruments.

Statistical Analysis

Data were analyzed using SPSS, version 28. Normality was checked by the Shapiro-Wilk test and homogeneity of variances by Levene's test. In addition, differences among the four groups were assessed using one-way analysis of variance (ANOVA). When a significant overall F was obtained, pairwise comparisons were performed using Tukey's honestly significant difference (HSD) post-hoc test. Further, effect sizes for ANOVA were reported as partial eta squared (η^2), and a $P < 0.05$ was considered statistically significant. All data are presented as means $\pm$ standard deviations.

Results

Vascular Endothelial Growth Factor

One-way ANOVA revealed a significant difference in VEGF protein expression among the four groups ($F [3, 20] = 180.22$, $P = 0.001$, $\eta^2 = 0.964$). Based on the results of post-hoc Tukey's HSD tests, the exercise + resveratrol group had significantly higher VEGF levels compared to control (mean difference [MD] = 0.57, $P = 0.001$), exercise-only (MD: 0.26, $P = 0.001$), and resveratrol-only (MD: 0.57, $P = 0.001$) groups. Likewise, the exercise-only group showed significantly higher VEGF than the control (MD: 0.30, $P = 0.001$) and resveratrol-only (MD: 0.31, $P = 0.001$) groups. Importantly, the resveratrol-only group did not substantially differ from the control group (MD: 0.001, $P = 0.99$), indicating that resveratrol alone was ineffective. The pattern of results, where the combined group exhibited the largest increase and resveratrol alone was inert, demonstrates a synergistic interaction between exercise and resveratrol on VEGF expression (Figure 1).

Follistatin-Like 1

A significant overall group effect was found for FSTL1 ($F [3, 20] = 381.53$, $P = 0.001$, $\eta^2 = 0.983$). Post-hoc comparisons (Table 2) indicated that the exercise +

Table 1. One-Way ANOVA Results for VEGF, FSTL1, and DIP2A

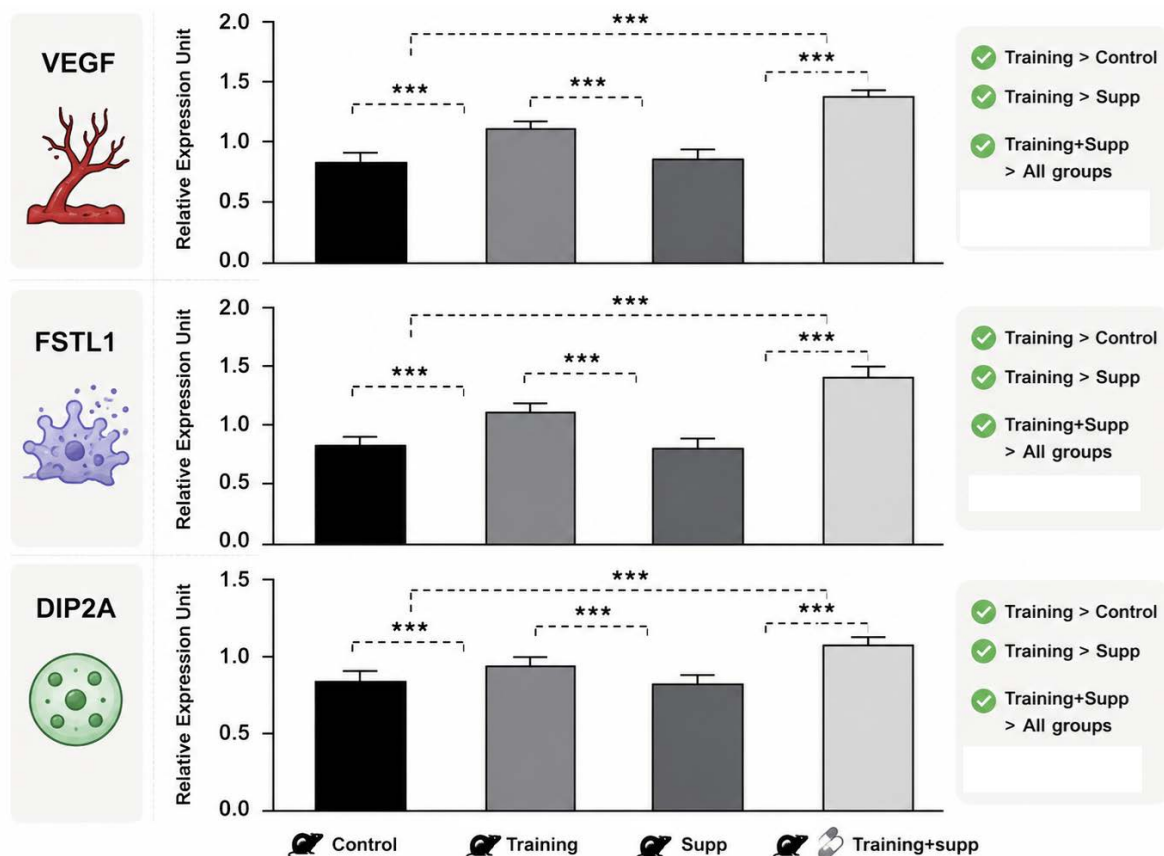
Variable	Sum of Squares	df.	Mean Square	F	P-Value
VEGF	36.1	3	0.45	180.22	0.001
FSTL1	41.1	3	0.47	381.53	0.001
DIP2A	0.33	3	0.11	220.87	0.001

Note: ANOVA: Analysis of variance; VEGF: Vascular endothelial growth factor; FSTL1: Follistatin-like 1; DIP2A: Disco-interacting protein 2 homolog A; df: Degree of freedom.

Table 2. Tukey's HSD Post-Hoc Pairwise Comparisons of Protein Expression Among Experimental Groups

Variable	Group 1	Group 2	Mean Difference	Standard Deviation	P-Value
VEGF	Control	Exercise	0.30	0.02	0.001
	Control	Supplement	0.001	0.02	0.99
	Control	Exercise+Supplement	0.57	0.02	0.001
	Exercise	Supplement	0.31	0.02	0.001
	Exercise	Exercise+Supplement	0.26	0.02	0.001
	Supplement	Exercise+Supplement	0.57	0.02	0.001
FSTL1	Control	Exercise	0.31	0.02	0.001
	Control	Supplement	0.006	0.02	0.47
	Control	Exercise+Supplement	0.58	0.02	0.001
	Exercise	Supplement	0.30	0.02	0.001
	Exercise	Exercise+Supplement	0.27	0.02	0.001
	Supplement	Exercise+Supplement	0.57	0.02	0.001
DIP2A	Control	Exercise	0.08	0.01	0.001
	Control	Supplement	0.003	0.01	0.99
	Control	Exercise+Supplement	0.28	0.01	0.001
	Exercise	Supplement	0.08	0.01	0.001
	Exercise	Exercise+Supplement	0.20	0.01	0.001
	Supplement	Exercise+Supplement	0.29	0.01	0.001

Note: VEGF: Vascular endothelial growth factor; FSTL1: Follistatin-like 1; DIP2A: Disco-interacting protein 2 homolog A; HSD: Honestly significant difference.

**Figure 1.** Effects of HIIT, Resveratrol, and Their Combination on VEGF, FSTL1, and DIP2A Protein Levels in Rat Heart Tissue

Note: *** $P < 0.001$ vs. all other groups. Refer to Table 2 for exact P -values. FSTL1: Follistatin-like 1; HIIT: High-intensity interval training; VEGF: Vascular endothelial growth factor; DIP2A: Disco-Interacting Protein 2 Homolog A

resveratrol group had remarkably higher FSTL1 levels than the control (MD: 0.58, $P = 0.001$), exercise-only (MD: 0.27, $P = 0.001$), and resveratrol-only (MD: 0.57, $P = 0.001$) groups. The exercise-only group was significantly higher

than the control (MD: 0.31, $P = 0.001$) and resveratrol-only (MD: 0.30, $P = 0.001$) groups in FSTL1 levels. Critically, resveratrol-only did not differ from the control (MD: 0.006, $P = 0.47$), implying that supplementation

alone had no effect. The fact that resveratrol markedly boosted FSTL1 only in the presence of exercise (exercise + resveratrol vs. exercise alone; MD: 0.27, $P=0.001$) confirms a synergistic effect (Figure 1).

Disco-Interacting Protein 2 Homolog A

Similarly, DIP2A protein levels considerably differed across groups ($F [3, 20]=220.87$, $P=0.001$, $\eta^2=0.971$). Tukey's HSD tests showed that the exercise + resveratrol group had significantly greater DIP2A expression than control (0.28, $P=0.001$), exercise-only (0.20, $P=0.001$), and resveratrol-only (0.29, $P=0.001$) groups. Moreover, exercise-only was substantially higher than control (0.08, $P=0.001$) and resveratrol-only (0.08, $P=0.001$) groups. Based on the results, resveratrol-only was not different from the control (0.003, $P=0.99$). Likewise, the combined group outperformed all others, and resveratrol's effect was only evident when combined with exercise, reinforcing the synergistic interaction (Figure 1).

Discussion

The results of the one-way ANOVA confirmed a significant overall difference in VEGF expression across the four groups. Based on Tukey's HSD post-hoc comparisons, the combined exercise + resveratrol group exhibited the greatest increase in VEGF, substantially exceeding that of all other groups. Furthermore, exercise alone significantly elevated VEGF levels compared with control and resveratrol-only groups, whereas resveratrol alone showed no significant difference from the control. This pattern, with the combination outperforming each intervention alone and resveratrol being ineffective by itself, clearly demonstrates a synergistic interaction between exercise and resveratrol on VEGF expression.

Likewise, Ghasemi et al examined the effect of combined training and resveratrol supplementation on the serum levels of adiponin, VEGF, NO, and gene expression of fibroblast growth factor-2 and angiostatin in rats with MI. They demonstrated that ten weeks of aerobic exercise and resveratrol supplementation led to increased levels of VEGF, adiponin, NO, and fibroblast growth factor-2 messenger RNA (mRNA) expression, along with decreased angiostatin levels in an MI rat model (16). Additionally, Qin et al investigated the effects of resveratrol on the VEGF pathway and apoptosis in frozen-thawed duck ovarian transplantation. They concluded that resveratrol significantly increased VEGF mRNA expression, decreased Bcl-2-associated X protein and Caspase-3 mRNA expression, and reduced the number of terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling-positive cells after cryopreservation and heterotopic ovarian transplantation. Resveratrol also improved antioxidant capacity (17). In our study, however, resveratrol alone failed to alter VEGF levels in the healthy aged heart, suggesting that its effects may depend on the presence of a co-stimulus (e.g., exercise or pathological stress). Regarding FSTL1 and DIP2A, our results revealed that exercise training

was the primary driver of their expression, with the combination group again showing the greatest increases. Post-hoc comparisons also confirmed that resveratrol markedly elevated FSTL1 and DIP2A only in the presence of exercise while having no effect alone, which conforms to the findings of Xi et al, demonstrating that dynamic resistance exercise increases skeletal muscle-derived FSTL1 and induces cardiac angiogenesis via the DIP2A–Smad2/3 pathway in rats after MI (6). Similarly, Chen et al reviewed evidence that regular exercise, especially that leading to cardiac repair after injury, increases FSTL1 expression in skeletal muscle and myocardium, thereby activating the TGF β /Smad2/3 pathway and enhancing angiogenesis (7).

Numerous studies have elucidated the mechanistic role of the FSTL1–DIP2A axis in angiogenesis. FSTL1 secreted from skeletal muscle can directly stimulate angiogenesis through the endothelial NOS pathway, inhibiting apoptosis while improving endothelial cell differentiation and migration (6). In vitro, FSTL1 increases AMPK phosphorylation in cultured vascular smooth muscle cells, reducing their proliferation and migration. Further, the TGF β 1–Smad2/3 signaling pathway is a major mechanism regulating angiogenesis, with its upstream member activin directly modulated by FSTL1, affecting TGF β receptor complex activity and downstream Smad2/3 phosphorylation. Notably, the adenoviral overexpression of FSTL1 accelerates angiogenesis in ischemic muscle but not in normoxic tissue, suggesting that FSTL1 function is context-dependent and linked to the endothelial cell niche (6).

In vivo and in vitro studies have also established DIP2A as the sole receptor for FSTL1. DIP2A is a membrane receptor protein with an intracellular domain, expressed in neurons, mesenchymal cells, endothelial cells, smooth muscle cells, and cardiomyocytes. Interference with DIP2A expression in cultured endothelial cells attenuates FSTL1-induced survival, migration, and tube formation, confirming that intracellular cascades triggered by FSTL1–DIP2A are key to angiogenesis regulation (18). Tania et al reported that the deletion of the *fstl1* gene in the vascular endothelium activates Smad1/5/8 signaling and upregulates bone morphogenetic protein/Smad-regulated genes (e.g., *jagged1*, *endoglin*, and *gata2*), leading to impaired pulmonary microvascular remodeling (20). Furthermore, TGF β 1 rapidly activates Smad, MAPK, and Akt pathways, but only Smad2/3 inhibition abolishes TGF β 1-induced FSTL1 expression (19), indicating that Smad2/3 acts downstream of FSTL1–DIP2A signaling with feedback regulation (19). Additional evidence from Liang et al demonstrated that the deletion of DIP2A in cultured cardiomyocytes reduces the protective effect of FSTL1 against anoxia/reoxygenation-induced apoptosis and decreases FSTL1-induced Akt phosphorylation (20). Moreover, anoxia–reoxygenation in cardiomyocytes simulates MI pathophysiology in vivo, and DIP2A activation by FSTL1 enhances downstream Akt signaling, which is critical for cardiomyocyte survival, apoptosis

inhibition, and myocardial fibrosis attenuation (21).

The observed synergy may reflect overlapping molecular pathways: exercise-induced AMPK activation and mild hypoxia stimulate FSTL1 expression (21), while resveratrol may facilitate a supportive anti-inflammatory environment via sirtuin 1/kappa-light-chain-enhancer of activated B cells (21). Although Akt and Smad2/3 phosphorylation were not directly measured, prior evidence indicates that FSTL1–DIP2A engagement activates these cascades (21), making it plausible that their combined amplification underlies the synergistic effect. This study was limited to protein-level data in healthy aged rats without functional angiogenic or cardiac endpoints; accordingly, translation to disease models or humans requires caution. Therefore, future work should incorporate functional outcomes and direct signaling measurements.

Conclusion

In aged rats, eight weeks of HIIT significantly increased cardiac VEGF, FSTL1, and DIP2A protein levels, while resveratrol alone had no measurable effect. Importantly, the combination of HIIT and resveratrol produced the highest increase in all three proteins, demonstrating a synergistic interaction. These preclinical findings suggest that resveratrol may serve as a useful adjunct to exercise in enhancing molecular pathways associated with angiogenesis in the aging heart. However, the study was limited to protein-level changes in healthy aged rodents, and further research incorporating functional vascular outcomes and diseased models is required before any clinical or broader physiological recommendations can be made in this regard.

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Artificial Intelligence Disclosure Statement

During the preparation of this manuscript, the authors employed a large language model (DeepSeek) for language editing, translation, grammatical editing, and stylistic refinement. All content generated with the assistance of this tool was precisely reviewed, validated, and revised by the authors in order to ensure accuracy, originality, and scholarly rigor. They assume full responsibility for the integrity and final content of the published article.

Authors' Contribution

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Writing–Review & Editing: Raheleh Raziee, Lida Moradi, Bahram Abedi, Mohammad Ali Azarbayjani

Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

This article has been derived from a PhD dissertation submitted to Islamic Azad University, Central North Branch (ethical code IR.IAU.TNB.REC.1403.277). All experimental procedures were approved by the institutional animal ethics committee and conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

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