



Adaptation of Endogenous Antioxidants Systems to Cumulative Weekly Exercise Dose: Exploring the Hormetic Threshold Between Oxidative Stress and Cellular Protection

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Abstract. Background/Objectives: Regular physical activity induces beneficial physio-logical adaptations; however, poorly programmed weekly training volumes may disrupt redox homeostasis and contribute to structural tissue damage. This study evaluates the dose–response relationship between cumulative weekly exercise loads and the systemic balance between oxidative stress markers and endogenous antioxidant defenses. Methods: Following PRISMA guidelines, this systematic review evaluated ex-perimental studies indexed in PubMed, Scopus, ScienceDirect, and DOAJ published between 2015 and 2024. After a rigorous three-stage eligibility screening process, 14 experimental studies met the predefined inclusion criteria and were included in the qualitative synthesis. Results: The synthesized evidence demonstrates a distinct biphasic hormetic response to physical exercise at the cellular level. Moderate cumulative training volumes (typically 150–300 min/week at submaximal intensities) consistently upregulate key endogenous antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), through redox-sensitive signaling pathways such as Nrf2 and PGC-1 α . Conversely, excessive or unaccustomed training volumes may overwhelm enzymatic defenses, resulting in sustained reactive oxygen species (ROS) overproduction, increased lipid peroxidation as reflected by malondialdehyde (MDA), and cellular maladaptation. Conclusion/Implications: These findings suggest the presence of a physiological threshold at which progressive exercise loading may optimize endogenous antioxidant adaptation while minimizing oxidative stress–induced cellular disruption. The evidence supports exercise-dose prescription strategies that integrate structured recovery periods as essential components for maintaining cellular integrity, adaptive capacity, and long-term physiological performance.

Keywords: Biphasic Hormesis, Antioxidant Enzymes, Oxidative Stress Markers, Redox Signaling Pathways, Exercise Dose Titration.

1 Introduction

1.1 Background and Urgency of The Research

Regular physical activity is widely recognized as a fundamental component of maintaining cardiovascular function, metabolic regulation, and cellular respiration. At the systemic level, these physiological adaptations are reflected by improved endothelial function, enhanced insulin sensitivity, and activation of anti-inflammatory signaling pathways, collectively contributing to a reduced risk of chronic disease. Nevertheless, the beneficial effects of exercise depend on the appropriate prescription of training load. Excessive training intensity or cumulative weekly training volume, particularly when implemented without adequate progression and recovery, may lead to a transient overproduction of reactive oxygen and nitrogen species (RONS) that exceeds the capacity of endogenous antioxidant defense systems. Persistent disruption of redox homeostasis may subsequently promote chronic oxidative stress, resulting in lipid peroxidation, oxidative modification of proteins, and DNA damage. Therefore, the overall health benefits of exercise are determined not by increasing training volume alone, but by achieving an appropriate balance among training dose, progressive overload, and adequate recovery[1], [2].

1.2 Research Gap

To date, the sports medicine and exercise physiology literature has provided substantial evidence regarding the effects of exercise on redox regulation; however, important inconsistencies remain. High-intensity exercise protocols, particularly high-intensity interval training (HIIT), have been widely reported to reduce oxidative stress biomarkers while enhancing the expression and activity of endogenous antioxidant enzymes. Nevertheless, considerable variability persists in the reported responses, largely due to differences in individual characteristics, including chronological age, baseline fitness level, and nutritional status. A major knowledge gap is the absence of a clear consensus regarding the hormetic threshold of cumulative weekly training volume, defined by the combined effects of training frequency, intensity, and duration, required to elicit beneficial cellular adaptations without disrupting redox homeostasis. The lack of quantitative evidence defining this optimal training dose limits the development of evidence-based exercise prescriptions for both athletic and clinical populations and may increase the risk of maladaptive responses, chronic fatigue, and exercise-induced tissue injury when training loads exceed an individual's adaptive capacity [1], [3], [4], [2], [5], [6].

1.3 Statement of Novelty and Originality

The originality of this study lies in its integrative molecular perspective, implemented through a systematic review conducted in accordance with the PRISMA 2020 guidelines. Unlike previous reviews that have primarily focused on the acute effects of single exercise sessions, the present study synthesizes evidence on the cumulative effects of [7], [8] weekly training load on cellular redox signaling. Its theoretical contribution is

the integration of current evidence describing the molecular pathways linking external exercise stimuli to the activation of key transcriptional regulators, including Nuclear Factor Erythroid 2–Related Factor 2 (Nrf2) and Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha (PGC-1 α). By systematically synthesizing findings from 14 high-quality experimental studies published between 2015 and 2026, this review identifies the range of weekly training loads associated with favorable redox adaptations, providing an evidence-based framework to inform future exercise prescription in both clinical and athletic settings [4], [2], [5].

1.4 Research Objectives

Specifically, this systematic review was designed to achieve the following objectives:

- To evaluate the effects of cumulative weekly training volume on the production of reactive oxygen species (ROS) and biomarkers of cellular oxidative stress.
- To examine the adaptive responses and regulatory mechanisms of the major endogenous antioxidant enzymes, particularly superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), in relation to variations in training frequency, intensity, and duration.
- To characterize the dose–response relationship between weekly training volume and redox homeostasis in order to identify the range of training loads associated with favourable physiological adaptations and enhanced cellular antioxidant capacity while minimizing oxidative damage.

2 RESEARCH METHODOLOGY

2.1 Research Design

This study employed a systematic literature review (SLR) to synthesize experimental evidence on the dose–response relationship between cumulative weekly training volume and endogenous antioxidant adaptations. To ensure methodological transparency, minimize the risk of selection bias, and enhance reproducibility, all stages of study identification, screening, eligibility assessment, and data extraction were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

2.2 Search Strategy and Data Sources

A comprehensive electronic literature search was conducted across four bibliographic databases: PubMed, Scopus, ScienceDirect, and the Directory of Open Access Journals (DOAJ). The search was limited to studies published between 2015 and 2026 to capture the most recent evidence in the field of molecular sports medicine.

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| ("training volume" OR "exercise dose" OR "intensity")
AND ("oxidative stress" OR "reactive oxygen species"
OR "MDA") AND ("endogenous antioxidants" OR "SOD" OR
"GPx" OR "catalase")
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Fig. 1. Search strategies were developed using Boolean operators as follows.

2.3 Inclusion and Exclusion Criteria

The following eligibility criteria were applied. Studies were included if they: (1) employed an experimental design, including randomized controlled trials (RCTs) and quasi-experimental studies, involving human participants of any age; (2) investigated structured exercise interventions with clearly quantified weekly training volume, including training frequency, intensity, and duration; and (3) reported outcomes related to oxidative stress biomarkers, such as malondialdehyde (MDA) and reactive oxygen species (ROS), together with the activity of major endogenous antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Studies were excluded if they: (1) used animal (in vivo) or cell culture (in vitro) models; (2) were narrative reviews or other non-original publications; (3) were not peer-reviewed; or (4) did not provide full-text access[11], [12], [13], [14], [15], [16].

2.4 Three Stage PRISMA Screening Workflow

The article selection process was conducted in three sequential stages of analysis. First, the initial identification stage yielded a total of 400 article records from all databases. Before formal screening, 80 articles were removed (50 due to duplication, 20 through automated screening, and 10 because of technical issues), leaving 320 articles for secondary evaluation. Second, during the title and abstract screening stage, 200 articles were excluded because they did not match the scope of the study. Of the remaining 120 records for which full-text articles were sought, 10 articles could not be retrieved, resulting in 110 articles available for comprehensive eligibility assessment. Third, during the final eligibility assessment stage, 110 full-text articles were rigorously evaluated against the predefined inclusion and exclusion criteria. At this stage, 83 articles were excluded for specific reasons: 40 articles were not directly related to the exercise dose–response relationship, 25 articles did not meet peer-review accreditation standards, and 18 articles did not provide full-text access. This screening process ultimately identified 14 high-quality experimental studies for qualitative synthesis.

3 RESULTS AND DISCUSSION

3.1 Structural Matrix of Reviewed Articles

All relevant data from the 14 included experimental studies were extracted and systematically organized into a standardized data extraction matrix to facilitate cross-study comparisons.

Table 1. Standardized Data Extraction and Coding Matrix of the Included Experimental Studies (n = 14)

No	Author & Year	Design & Sample	Intervention & Weekly Dosage	Oxidative Markers	Endogenous Antioxidant Outcomes
1	Meng & Su (2024)	Comprehen-sive Review / General Popu-lation	Macro-Evalu-ation of Load: Cumulative vs. Acute	Systemic ROS	Total Enzy-matic Balance
2	Zhou et al. (2022)	Meta-analysis / Healthy Adults	Exposure Var-iation: Cumulative Training	Intracellular Oxidative Stress	Adaptive Enzy-matic Response
3	Powers et al. (2020)	Mechanistic Study / Cellular & Human	Load Modula-tion: Progressive Cumulative	Biphasic ROS Signaling	Nrf2 & NF-κB Transcription
4	Malan et al. (2024)	Experimental / Recreational Runners	Routine Mod-erate Exercise vs. Acute Re-sistance	Pro-inflam-matory Lipids	Anti-Inflamma-tory Balance
5	Reljic (2025)	Clinical Trial / Cohort	High-Inten-sity Interval Training (HIIT)	Systemic Oxidative Stress	Upregulation of SOD, GPx, & CAT
6	Lu et al. (2021)	Systematic Review / Non-athlete Cohort	High-Inten-sity Sessions Without Con-ditioning	Acute Oxi-dative Surge	Compensation for Enzymatic Def-icit
7	Awang Daud et al. (2022)	Experimental / Cohort Cycling	Cycling Inten-sity & Duration Var-iation	ROS Fluc-tuations Per Session	Dose-Depend-ent Modulation
8	Clemente-Suárez et al. (2023)	Performance Study / Elite Athletes	Scheduled & Patterned Athletic Training	Perfor-mance-Re-lated ROS Bal-ance	Maximal Cellu-lar Resilience
9	Vargas-Mendoza et al. (2021)	Nutritional Framework / Active Adults	Mitochondrial Modulation & Diet	Regulation of Oxidative Stress	Oxidative Phosphoryla-tion Efficiency
10	Ye et al. (2021)	Meta-analysis / Older Adults	Structured Moderate Aerobic Pro-tocol	Reduction in Chronic Markers	Optimized Cel-lular Protection
11	de Lima et al. (2021)	Experimental / non-athlete Men	Resistance Training + Blood Flow	Immune Cell Apoptosis	Atypical Oxi-dative Response

3.2 Deconstruction of the Nrf2/PGC-1α Reciprocal Regulatory Pathway

A qualitative synthesis of all the data convincingly shows that the adaptation of endogenous antioxidant enzymes to weekly exercise doses is tightly controlled by redox-sensitive molecular networks that work in a biphasic manner. When the weekly physical load is kept within a physiological comfort zone (sweet spot, averaging 150-300 minutes per week at submaximal intensity), transient increases in ROS levels won't damage cell structures. On the contrary, these moderate free radical concentrations act as a crucial second messenger to activate protective transcription cascades. The latest scientific evidence indicates that if a single acute exercise session only triggers a transient spike lasting about 24 hours, then consistent and regular weekly exercise stimuli will turn that short-term signal into a stable accumulation of protective proteins at baseline levels[1], [7], [8].

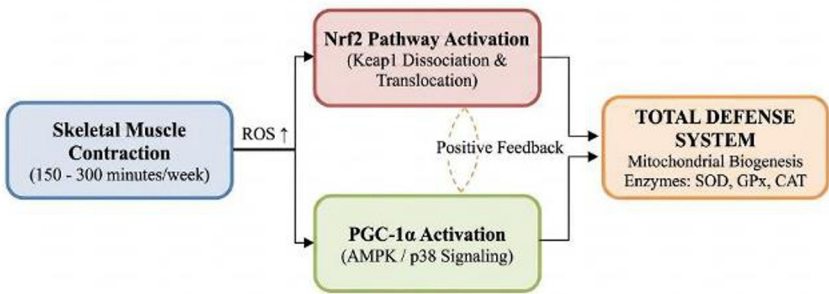


Fig. 2. The Interaction Mechanism of Positive Feedback Between the Nrf2 and PGC-1α Pathways in Inducing Mitochondrial Biogenesis and Antioxidant Enzymes Due to Measured Exercise Stimuli.

Mechanistically, the main pathway that dictates the upregulation of these enzymes is controlled by Nrf2. Under resting (basal) conditions, Nrf2 is tightly bound in the cytoplasm by its repressor protein, Kelch-like ECH-associated protein 1 (Keap1). However, moderate ROS induction from programmed muscle contractions will oxidize specific cysteine residues on Keap1. This oxidation changes Keap1's three-dimensional conformation, causing Nrf2 to be released so it can freely move directly into the cell nucleus. Inside the nucleus, Nrf2 specifically binds to the Antioxidant Response Element (ARE) on the promoter region of target genes, triggering massive transcription of genes encoding primary endogenous antioxidant enzymes: SOD, GPx, and CAT[7], [8].

This cellular shield is boosted synergistically through the simultaneous activation of PGC-1α, the master regulator of mitochondrial lifecycle and cellular energy adaptation. Repeated muscle contractions in a structured weekly cycle will increase the intracellular AMP/ATP ratio, activating AMP-activated protein kinase (AMPK) as well as p38 mitogen-activated protein kinase (p38 MAPK). Both kinases phosphorylate and activate PGC-1α. Once active, PGC-1α drives the biogenesis of new mitochondria to optimize energy efficiency and minimize electron leakage, while interacting with nuclear

transcription factors to ramp up the expression of manganese superoxide dismutase (MnSOD/SOD2) and catalase directly in the mitochondrial matrix[8], [6], [17].

A new theoretical breakthrough that's super important in the world of sports biochemistry is the discovery of a two-way mutual regulatory feedback loop between these two tissues. PGC-1 α acts as an upstream metabolic sensor that directly boosts the transcription of the Nrf2 gene. At the same time, the promoter region of the PGC-1 α gene has been shown to have two high-affinity ARE binding sites. As a result, Nrf2 molecules that manage to enter the nucleus will immediately latch onto the PGC-1 α promoter to boost its expression. This synergy creates a self-amplifying circuit that keeps enhancing the cell's antioxidant capacity[8].

On the other hand, data analysis in groups with excessively high weekly training volumes without scheduled recovery blocks shows a completely damaging scenario. When the hyper-generation of ROS exceeds enzymatic saturation limits, endoplasmic reticulum stress occurs. These destructive free radical concentrations trigger severe cellular stress and push chronic pro-inflammatory signaling through massive NF- κ B activation. This massive oxidative damage eventually degrades the physical structure of the antioxidant enzymes themselves, triggers intense lipid peroxidation (marked by a sharp spike in serum MDA levels), and collapses the basic functionality of SOD and CAT. Therefore, the antioxidant benefits of exercise are non-linear; optimizing tissue protection requires precisely titrated training loads to oxidize Keap1 and activate the Nrf2/PGC-1 α feedback loop without damaging the structural integrity of cell membranes[1], [3], [4], [9], [10].

4 CONCLUSION AND RECOMMENDATIONS

4.1 Conclusion

The accumulation of weekly training doses has an inverted U-shaped non-linear relationship, which is modeled as a biphasic hormesis curve, with the cellular antioxidant defense infrastructure. Weekly training loads managed within a moderate range (150 to 300 minutes per week at submaximal intensity) act as positive stressors. This controlled ROS signaling triggers structural activation of the Nrf2 factor and the PGC-1 α coactivator, which synergistically boost the synthesis of key defense enzymes (SOD, GPx, CAT) to ensure cell safety [1], [7], [8], [17] [11]. On the other hand, massive training volumes without enough rest will disrupt redox homeostasis, damage enzymatic structures, accelerate lipid peroxidation (MDA spikes), and activate pro-inflammatory NF- κ B cascades. In the end, boosting antioxidant protection is not an automatic result of just doing physical activity; it is a highly sensitive biological response that is fully controlled by how pre-cisely the exercise is dosed[1], [3], [4], [9], [10].

4.2 Practical Recommendations and Future Research Directions

Clinical Implications and Athletic Coaching: Sports medicine practitioners, fitness coaches, and clinical instructors should ditch the rigid, one-size-fits-all exercise prescription approach. Weekly training dose determinations must be personalized, consid-

ering chronological age, nutritional status, and basic metabolic capacity as key parameters that shouldn't be overlooked. The design of training periodization should include structured recovery blocks between high-volume sessions to give cells enough time to synthesize new enzymatic proteins[1], [11], [2], [6].

Blueprint for Future Research: Future researchers are encouraged to move from observational cross-sectional study designs to multi-year longitudinal randomized controlled trials (RCTs) to monitor redox shifts in real time. Parameter measurements should adopt advanced and objective biomarkers, including Total Antioxidant Capacity (TAC), advanced DNA damage markers (8-OHdG), and direct analysis of Nrf2 protein expression in peripheral blood mononuclear cells (PBMCs). Finally, multidisciplinary comparative studies are needed to isolate specific hormesis thresholds across various modern exercise modalities, such as comparing high-volume HIIT with low-intensity resistance training combined with blood flow restriction (BFR) techniques[7], [5].

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