



Nigella Sativa Supplementation Modulates Exercise-Induced Oxidative Stress and Inflammation: A Randomized Controlled Trial

Roy Januardi IRAWAN^{1*} Heri WAHYUDI¹ Mokhamad Nur BAWONO¹
Ananda Perwira BAKTI¹ Nanda RIMAWATI¹ Abdul Rohim TUALEKA²

¹Sports Science Department, Sports Science and Health Faculty, Universitas Negeri Surabaya, Surabaya, Indonesia.

²Department of Occupational Health and Safety, Faculty of Public Health, Airlangga University, Surabaya.

ABSTRACT

Keywords

Exercise,
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inflammation,
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Intense physical exercise can lead to oxidative stress and inflammation, which may impair muscle recovery and athletic performance. *Nigella Sativa* (*N. sativa*) possesses antioxidant and anti-inflammatory properties, however, limited studies have examined its effects on oxidative stress and inflammation biomarkers post-exercise. This randomized, double-blind, placebo-controlled trial investigated the impact of *N. sativa* supplementation on malondialdehyde (MDA) and high-mobility group box 1 (HMGB1) levels following eccentric exercise. Forty-two recreationally active males (aged 18–21 years) were randomly assigned to either the *N. sativa* group (500 mg/day, n=21) or the placebo group (starch capsules, n=21) for 28 days. After supplementation, participants performed a standardized eccentric step-down protocol to induce muscle damage, and blood samples were collected at three time points: pre-exercise (T0), immediately post-exercise (T1), and 24 hours post-exercise (T2). MDA and HMGB1 levels significantly increased post-exercise (T1) in both groups ($p < 0.001$); however, the *N. sativa* group exhibited significantly lower MDA and HMGB1 levels compared to the placebo group at T1 and T2 ($p < 0.001$). These findings suggest that *N. sativa* supplementation may play a protective role against exercise-induced muscle damage by mitigating oxidative stress and inflammation. Further research is warranted to explore long-term effects and optimal dosages in athletic populations.

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*Corresponding Author:

Roy Januardi IRAWAN
E-mail Address:
royjanuardi@unesa.ac.id

INTRODUCTION

Regular exercise offers numerous positive effects, including enhanced cardiovascular health, improved metabolic function, and strengthened immune response (Hyldahl & Hubal, 2014). These benefits contribute to overall well-being and longevity when balanced with proper recovery strategies. However, high-intensity or prolonged exercise, such as endurance training, resistance training with excessive loads, or repeated bouts of exhaustive exercise, can induce oxidative stress and inflammation (Wadley et al., 2019), which can impact muscle recovery and overall physiological function (Suzuki, 2021).

During intense exercise, increased oxygen consumption leads to the overproduction of reactive oxygen species (ROS) in mitochondria (Bouviere et al., 2021). While moderate levels of reactive oxygen species (ROS) play a role in cellular signaling and adaptation, excessive ROS can damage cellular components, including lipids, proteins, and DNA (Jomova et al., 2023). This oxidative stress primarily arises from electron leakage in the mitochondrial electron transport chain (ETC) resulting in the formation of superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) (Nandi et al., 2019). Normally, endogenous antioxidant systems, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), help neutralize oxygen species (ROS) (Fernández-Lázaro et al., 2020). However, during prolonged or high-intensity exercise, the antioxidant defense mechanisms may become overwhelmed, resulting in oxidative damage and lipid peroxidation (Bicer et al., 2018).

In addition to oxidative stress, excessive ROS generation also triggers an inflammatory response through the activation of nuclear factor-kappa B (NF- κ B) signaling (Jomova et al., 2023; Xie et al., 2024). ROS promote the release of damage-associated molecular patterns (DAMPs), including High Mobility Group Box 1 (HMGB1) (Tu & Li, 2023), which interacts with Toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE). These pathways activate NF- κ B, leading to the upregulation of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β) (Choi et al., 2019; Jomova et al., 2023; C.-H. Lin et al., 2021). The sustained elevation of these inflammatory mediators can impair muscle recovery, contribute to tissue damage, and reduce training adaptations.

Over time, chronic oxidative stress and persistent inflammation can have long-term consequences on an athlete's health and performance. Prolonged exposure to elevated oxygen species (ROS) and inflammatory cytokines has been linked to muscle degeneration, an increased risk of overuse injuries, impaired immune function, and even the development of

chronic diseases, including cardiovascular disorders and metabolic dysfunctions (Bjørklund et al., 2022). Additionally, chronic inflammation may reduce training efficiency by impairing muscle adaptation and recovery, ultimately leading to decreased performance and increased fatigue (Massaro et al., 2019).

To counteract oxidative stress and inflammation, athletes often employ various recovery strategies, including antioxidant supplementation, adequate nutrition (Ayubi et al., 2024), hydration, cryotherapy, and rest. Dietary antioxidants, such as vitamins C and E (Patel et al., 2020; Righi et al., 2020), polyphenols (Huang et al., 2021), and omega-3 fatty acids (O'Connor et al., 2022) are commonly used to neutralize excess oxygen species (ROS). Additionally, strategies such as active recovery, massage (Heiss et al., 2019), and ice baths aim to reduce inflammation and promote muscle healing (Yoshida et al., 2022). While these interventions can support recovery, excessive antioxidant intake may blunt beneficial training adaptations by interfering with endogenous antioxidant defense mechanisms.

Malondialdehyde (MDA) is a well-established biomarker of lipid peroxidation (Pyne, n.d.), while High Mobility Group Box 1 (HMGB1) (Choe et al., 2018) is a pro-inflammatory mediator involved in cellular stress responses. HMGB1 is particularly relevant in exercise-induced oxidative stress as it functions as an alarmin released by stressed or damaged cells, triggering inflammatory pathways through Toll-like receptor 4 (TLR4) and receptor for advanced glycation end products (RAGE) (L. Lin et al., 2022). Unlike other inflammatory markers such as TNF- α and IL-6, which are primarily secreted by immune cells, HMGB1 is directly associated with cellular damage and prolonged inflammatory responses (Ta Na et al., 2022). Elevated HMGB1 levels post-exercise may indicate delayed recovery and excessive inflammatory activation, making it a crucial biomarker for evaluating the impact of oxidative stress and potential interventions (Ottestad et al., 2019).

Despite well documented impact of oxidative stress and inflammation on athletic performance, a significant gap remains in understanding effective natural interventions to mitigate these adverse effects. Several studies have explored the antioxidant and anti-inflammatory properties of *Nigella Sativa* (*N. sativa*) in various health conditions (Akil et al., 2011; Jakubczyk et al., 2025). Commonly known as black seed, *N. sativa* is a medicinal plant traditionally used for numerous therapeutic purposes. However, there is often ambiguity in the literature regarding which part of the plant exerts the most significant effect – whether the whole plant or specifically the seeds. Contemporary research, however, increasingly

emphasizes that the seeds of *N. sativa* are the most bioactive component, owing to their high concentrations of thymoquinone, nigellone, and polyphenolic compounds.

These bioactive compounds are primarily responsible for the potent antioxidant and anti-inflammatory effects attributed to *N. sativa* seed extracts, positioning them as a promising candidate for mitigating exercise-induced oxidative stress and inflammation. Despite this, studies specifically examining the effects of *N. sativa* seeds on oxidative stress biomarkers, such as malondialdehyde (MDA), and inflammatory mediators like high-mobility group box 1 (HMGB1) in the context of eccentric exercise remain limited.

Moreover, most previous studies have focused on the effects of *N. sativa* in pathological conditions or animal models, leaving a gap in clinical evidence supporting its use as a natural recovery strategy for athletes and physically active individuals. The specific mechanisms by which *N. sativa* seeds modulate oxidative stress and inflammation post-exercise are also not yet fully understood, particularly about molecular interactions within the NF- κ B signalling pathway and the regulation of endogenous antioxidant defences.

The findings of this study could have significant implications for both sports science and clinical applications. Suppose If *N. sativa* seeds supplementation proves to be effective. In that case, it may serve as a natural, accessible, and safe alternative for athletes and physically active individuals in managing oxidative stress and inflammation, potentially enhancing post-exercise recovery and overall performance. Moreover, these results contribute to the broader understanding of plant-based interventions in exercise physiology, highlighting their role in supporting muscle recovery and mitigating exercise-induced cellular damage. This study may also inspire future research on natural antioxidants, paving the way for more evidence-based applications in sports nutrition and long-term athletic health.

Given the increasing interest in natural supplementation for enhancing recovery and performance, this study aims to provide scientific evidence on the efficacy of *N. sativa* in modulating oxidative stress and inflammation. By evaluating its effects on MDA and HMGB1 levels following exercise, this study aims to determine whether *N. sativa* supplementation can serve as a viable strategy to support recovery, reduce exercise-induced cellular stress, and optimize athletic performance.

METHODS

Participants

This study employed a randomized, double-blind, placebo-controlled design to

evaluate the effects of *N. sativa* seed capsule supplementation on oxidative stress and inflammation post-exercise. Participants were selected using purposive sampling from recreationally active male students of the Sports Science Department, Universitas Negeri Surabaya, aged 18–21 years, who met the following inclusion criteria:

- Male, recreationally active, and healthy
- Normal Body Mass Index (BMI)
- Non-smokers and not taking any medications or dietary supplements during the study
- Willing to abstain from high-intensity physical activity throughout the study period

The required sample size was determined based on a power analysis (80% power, $\alpha = 0.05$) to ensure statistical significance. A total of 42 participants were randomly assigned in a 1:1 ratio to either the *N. sativa* group ($n = 21$) or the placebo group ($n = 21$):

- *N. sativa* group: Received 500 mg/day of *N. sativa* seed extract in capsule form for 28 days. The supplement used in this study was a commercially available soft gel capsule containing standardized *N. sativa* seed extract, as indicated on the product label. Each capsule contained 500 mg of seed extract, including a quantified amount of 15 mg thymoquinone (TQ) per capsule, standardized by the manufacturer.
- Placebo group: The placebo capsules contained 500 mg of starch powder.

Participants were instructed to consume one capsule daily in the morning with water. Participants in the experimental group consumed one capsule daily for 28 days at the same time each day to maintain consistency. Compliance was monitored weekly through direct supervision and capsule count assessments. All participants provided written informed consent before enrolment.

Participants were instructed to refrain from engaging in additional physical activity, taking anti-inflammatory drugs, or using dietary supplements throughout the study. The study was conducted under controlled laboratory conditions to minimize external influences on oxidative stress and inflammation markers.

Procedures

This study employed a randomized, double-blind, placebo-controlled, pretest-posttest design with control group, assessing the effects of 28-day *N. sativa* supplementation on MDA (an oxidative stress marker) and HMGB1 (an inflammation marker) following intense eccentric exercise.

The research spanned 30 days, beginning with an initial evaluation on Day 1 to assess baseline characteristics (body weight, height, fat percentage, physical activity level, and

VO₂max). Throughout the study, participants were restricted from engaging in any exercise except for the experimental session.

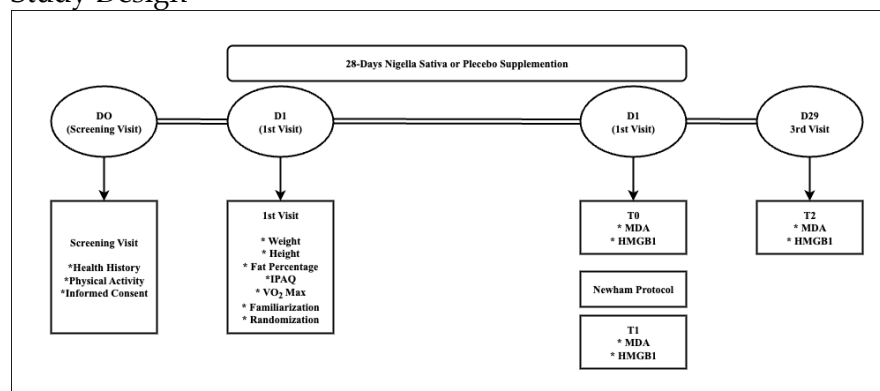
During the screening visit (Day 0), participants completed a physical fitness form that detailed their weekly running frequency, training volume, injury and illness history, and recent medication use.

The 28-day supplementation period required participants to consume one capsule per day while maintaining their usual diet and avoiding additional supplementation or anti-inflammatory medications. Compliance was monitored weekly through direct supervision and self-reported logs.

On Day 28, participants performed a modified version of the Newham protocol (Newham et al., 1983), a single-bout step-down eccentric exercise, to assess exercise-induced inflammation. The protocol involved stepping down from a 40 cm bench at a pace of 15 steps per minute, guided by a metronome, for a total duration of 10 minutes, divided into five sets of 2 minutes each, with 30-second rest intervals between sets. The eccentric movement induced muscle micro-tears, leading to oxidative stress and inflammation (Guadagnin et al., 2022).

Throughout the 30-day study period, participants remained uninjured, refrained from all physical activity, and were instructed not to consume anti-inflammatory drugs, treatments, or additional dietary supplements. A summary of the study design is presented in Figure 1.

Figure 1.
Study Design



Blood Sample Collection

Blood samples were collected at three time points:

1. T0 (1 hour before exercise) – Baseline measurement.
2. T1 (Immediately post-exercise) – To assess acute exercise-induced changes.
3. T2 (24 hours post-exercise) – To evaluate the delayed inflammatory response.

Blood sampling procedure was conducted at three time points: before exercise (T0), immediately after exercise (T1), and 24 hours post-exercise (T2). Blood samples were drawn from the cubital vein using a sterile needle, with approximately 5 mL collected at each time point. The collected blood was placed in EDTA tubes to prevent coagulation and immediately centrifuged at 3000 rpm for 15 minutes to separate plasma. The obtained plasma was stored at -20°C until further analysis using the ELISA method to measure MDA and HMGB1 levels. All procedures were performed by trained medical personnel under aseptic conditions to minimize the risk of contamination or measurement errors (Bloomer, 2008; Powers et al., 2010). All laboratory analyses were conducted at the Sports Science Laboratory, Universitas Negeri Surabaya, and the Faculty of Public Health Laboratory, Airlangga University.

Data Analysis

All statistical analyses were performed using SPSS version 23. Descriptive statistics were presented as mean $\pm$ standard deviation (SD).

The Shapiro–Wilk test was used to assess the normality of data distribution for MDA and HMGB1 levels, and the Levene's test was used to evaluate the homogeneity of variances between groups. The results showed that all variables were normally distributed and exhibited equal variances across groups and time points ($p > 0.05$), thereby satisfying the assumptions required for parametric testing.

A two-way repeated-measures ANOVA was used to analyze the effects of time (T0, T1, T2), group (*N. sativa* vs. Placebo), and their interaction on MDA and HMGB1 levels. If a significant main or interaction effect was found, Bonferroni post-hoc tests were conducted for pairwise comparisons.

Additionally, independent t-tests were applied to compare MDA and HMGB1 levels between groups at each time point. A Bonferroni correction was applied to control for multiple comparisons, adjusting the significance threshold to $p < 0.0167$. A p -value < 0.05 was considered statistically significant for all other analyses.

RESULTS

Respondent Characteristics

A total of 42 male recreational students from the Sports Sciences Department at Universitas Negeri Surabaya participated in this study. Participants were randomly assigned to either the *N. sativa* supplementation group ($n = 21$) or the placebo group ($n = 21$). The overall mean age was 19.55 ± 0.83 years, with the *N. sativa* group averaging 19.43 ± 0.87 years and the

placebo group 19.67 ± 0.80 years. The mean BMI of all participants was 21.13 ± 0.67 kg/m². The *N. sativa* group had a mean BMI of 21.04 ± 1.23 kg/m², while the placebo group had 21.22 ± 1.19 kg/m².

Table 1 presents the baseline characteristics of both groups, including weight, BMI, body fat percentage, IPAQ score, VO₂max, and lean body mass (LBM). These baseline values confirm that the groups were well-matched, ensuring that any observed differences in later analyses are attributable to *N. sativa* supplementation rather than pre-existing variations.

Table 1.
Baseline Characteristics of Participants in *Nigella Sativa* and Placebo Groups

Variable	<i>N. sativa</i> Group (n=21)	Placebo Group (n=21)	<i>p</i> -values
Weight (kg)	59.29 $\pm$ 3.81	60.19 $\pm$ 5.04	0.759
BMI (kg/m ²)	21.04 $\pm$ 1.23	21.22 $\pm$ 1.19	0.957
Body Fat (%)	18.93 $\pm$ 0.63	17.30 $\pm$ 0.63	0.967
Physical Activity Level (IPAQ, MET-min/week)	1221.93 $\pm$ 220.26	1251.36 $\pm$ 207.00	0.222
VO ₂ max (mL/kg/min)	38.25 $\pm$ 2.23	35.17 $\pm$ 2.19	0.535
Lean Body Mass (kg)	48.05 $\pm$ 2.99	49.77 $\pm$ 4.12	0.745

Note. All data are presented as means $\pm$ SD; no significant differences were found between the *Nigella sativa* and placebo groups at baseline ($p > 0.05$ for all variables).

Table 1 shows no significant baseline differences between the *N. sativa* and placebo groups ($p > 0.05$), confirming that the groups were comparable prior to the intervention. This supports the validity of attributing subsequent effects to the supplementation.

Oxidative Stress Assessment Result

Malondialdehyde (MDA), a biomarker of oxidative stress and lipid peroxidation, was measured at three time points: 1 hour before exercise (T0), immediately after exercise (T1), and 24 hours post-exercise (T2). The mean plasma levels of MDA for both *N. sativa* and Placebo groups across these time points are shown in Table 2.

Table 2.
Plasma MDA Levels Across Time Points and Pairwise Comparisons

Group	Time Point	MDA (μ mol L ⁻¹)	Pairwise Comparison	P-value (Bonferroni adjusted)
<i>N. sativa</i>	1 hour before (T0)	2.65 $\pm$ 0.08	T0 vs T1	< 0.001
	Immediately after (T1)	4.54 $\pm$ 0.15	T0 vs T2	< 0.001
	24 hours post (T2)	3.13 $\pm$ 0.15	T1 vs T2	< 0.001
Placebo	1 hour before (T0)	2.75 $\pm$ 0.08	T0 vs T1	< 0.001
	Immediately after (T1)	6.13 $\pm$ 0.17	T0 vs T2	< 0.001
	24 hours post (T2)	4.33 $\pm$ 0.18	T1 vs T2	< 0.001

Note. Values are means $\pm$ SD. All pairwise comparisons between time points within each group were statistically significant after Bonferroni adjustment ($p < 0.001$).

As shown in Table 2, MDA levels increased significantly in both groups immediately after exercise (T1) compared to baseline (T0) ($p < 0.001$). However, the increase was significantly attenuated in the *N. sativa* group. By 24 hours post-exercise (T2), MDA levels had decreased in both groups but remained significantly lower in the *N. sativa* group ($p < 0.001$).

The Bonferroni-adjusted post-hoc comparisons showed significant differences across all time points in both groups (T0 vs T1, T0 vs T2, and T1 vs T2; all $p < 0.001$), indicating a consistent pattern of oxidative stress response and recovery.

These results suggest that *N. sativa* supplementation may attenuate exercise-induced oxidative stress and promotes faster recovery toward baseline MDA levels.

Inflammation Assessment Result

HMGB1 is used as a biomarker of inflammation and cellular stress following intense exercise. Its plasma levels were measured at T0, T1, and T2, as shown in Table 3.

Table 3.
Plasma HMGB1 Levels Across Time Points and Pairwise Comparisons

Group	Time Point	HMGB1 (ng mL ⁻¹)	Pairwise Comparison	P-value (Bonferroni adjusted)
<i>N. sativa</i>	1 hour before (T0)	1.11 ± 0.02	T0 vs T1	< 0.001
	Immediately after (T1)	2.45 ± 0.06	T0 vs T2	< 0.001
	24 hours post (T2)	1.87 ± 0.04	T1 vs T2	< 0.001
Placebo	1 hour before (T0)	1.14 ± 0.04	T0 vs T1	< 0.001
	Immediately after (T1)	2.87 ± 0.08	T0 vs T2	< 0.001
	24 hours post (T2)	2.35 ± 0.05	T1 vs T2	< 0.001

Note. HMGB1 values are presented as means ± SD. Pairwise comparisons between time points (T0, T1, T2) within each group were performed using Bonferroni-adjusted post hoc tests. All comparisons were statistically significant ($p < 0.001$).

As shown in Table 3, HMGB1 levels increased significantly immediately after exercise (T1) in both groups ($p < 0.001$). However, the *N. sativa* group exhibited a significantly smaller increase compared to the placebo group. By 24 hours post-exercise (T2), HMGB1 levels had decreased in both groups, with a significantly greater reduction observed in the *N. sativa* group ($p < 0.001$).

These results suggest that *N. sativa* supplementation may attenuate the inflammatory response induced by intense physical exercise and facilitate faster recovery of HMGB1 levels. Bonferroni-adjusted post-hoc tests confirmed significant changes between all time points ($p < 0.001$), supporting *N. sativa*'s anti-inflammatory effect in modulating HMGB1 response post-exercise.

Effectiveness of *N. sativa* Supplementation

To further evaluate the effectiveness of *N. sativa* supplementation in attenuating exercise-induced oxidative stress and inflammation, independent sample t-tests were conducted to compare MDA and HMGB1 levels between the *N. sativa* and placebo groups at each time point (T0, T1, and T2). The results are shown in Table 4.

Table 4.
Independent t-Test Results Comparing *N. sativa* and Placebo Groups.

Variable	Time Point	t-statistic	p-value	Significance
MDA	T0	0.622	p = 0.537	No
MDA	T1	4.663	p < 0.001	Yes
MDA	T2	5.058	p < 0.001	Yes
HMGB1	T0	2.900	p = 0.006	Yes
HMGB1	T1	19.466	p < 0.001	Yes
HMGB1	T2	33.816	p < 0.001	Yes

Note. Data represent results from two-way repeated measures ANOVA examining the interaction effect between group (*Nigella sativa* vs. placebo) and time (T0 = 1 h before exercise, T1 = immediately after exercise, T2 = 24 h post-exercise). Statistical significance was set at $p < 0.05$.

The results show no significant difference in MDA levels between groups at baseline (T0), confirming homogeneity prior to intervention. However, significant differences were found at T1 and T2 ($p < 0.001$), indicating that *N. sativa* effectively reduced MDA levels compared to placebo following exercise and during recovery.

Notably, HMGB1 levels differed slightly at baseline (T0; $p = 0.006$), but the gap between groups widened substantially at T1 and T2. This suggests that *N. sativa* has a notable impact in limiting the post-exercise inflammatory response.

While HMGB1 levels were significantly different at baseline (T0; $p = 0.006$), the magnitude of difference increased substantially after exercise (T1 and T2), suggesting a pronounced modulatory effect of *N. sativa* on the inflammatory response. The larger effect observed post-exercise indicates a potential modulatory role of *N. sativa* on the acute inflammatory response. These t-test findings support the significant group $\times$ time interactions found in the repeated-measures ANOVA.

To further explore the overall trend across time and between groups, a two-way repeated measures ANOVA was conducted to assess the interaction effect of group $\times$ time.

The ANOVA results reveal a statistically significant interaction between group and time for both MDA and HMGB1 ($p < 0.001$). This indicates that the pattern of biomarker changes across time points was significantly different between the *N. sativa* and placebo groups.

Together, these findings strengthen the evidence that *N. sativa* supplementation attenuates the physiological impact of intense exercise by reducing oxidative stress and inflammatory responses, particularly during the acute and 24-hour post-exercise phases. Overall, this study supports the potential role of *N. sativa* as a natural supplement to mitigate exercise-induced oxidative and inflammatory stress. Further studies with larger and more diverse populations are warranted to validate and expand these findings.

Table 5.

Two-Way Repeated Measures ANOVA (Group $\times$ Time Interaction).

Variable	Effect	F-statistic	<i>p</i> -value	Significant
MDA	Group $\times$ Time	41.61	< 0.001	Yes
HMGB1	Group $\times$ Time	105.62	< 0.001	Yes

Note. Data represent results from two-way repeated measures ANOVA examining the interaction effect between group (*Nigella sativa* vs. placebo) and time (T0 = 1 h before exercise, T1 = immediately after exercise, T2 = 24 h post-exercise). Statistical significance was set at $p < 0.05$.

DISCUSSION

The findings of this study demonstrate that *Nigella Sativa* seed supplementation significantly reduces oxidative stress (MDA) and inflammation (HMGB1) following exercise compared to placebo. The observed effects were time-dependent, with the most pronounced differences occurring immediately post-exercise (T1) and persisting 24 hours post-exercise (T2). These results highlight the potential of *N. sativa* seed extract as an antioxidant and anti-inflammatory supplement for enhancing post-exercise recovery.

Intense physical exercise is known to increase the production of reactive oxygen species (ROS) due to heightened mitochondrial activity, increased oxygen consumption, and activation of enzymatic oxidases such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Di Meo et al., 2019; Jomova et al., 2023). During exercise, muscle contractions lead to higher metabolic demands, which accelerate electron leakage from the mitochondrial electron transport chain (ETC) (Matta et al., 2021). This results in the formation of superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2), both of which contribute to oxidative stress and lipid peroxidation (Sawada et al., 2023).

In addition to oxidative stress, exercise induces an inflammatory response through muscle microdamage, mechanical stress, and increased cytokine production (Middelbeek et al., 2021; Volpe-Fix et al., 2023). The breakdown of muscle fibers triggers the release of damage-associated molecular patterns (DAMPs) (Slavin et al., 2024), including HMGB1 (Li et al., 2023), which subsequently activates the toll-like receptor (TLR) and NF- κ B pathways (Syukri et al., 2022). This activation promotes the release of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β (Thirupathi et al., 2021), leading to a systemic inflammatory response that persists for several hours post-exercise. If not properly regulated, prolonged oxidative stress and inflammation can impair muscle recovery, induce fatigue, and reduce athletic performance.

Our study confirms this effect, as seen in the significant increase in MDA and HMGB1 levels post-exercise (T1) in the Placebo group. However, *N. sativa* supplementation attenuated these increases, suggesting its potential role in mitigating exercise-induced oxidative damage and inflammation. These findings align with previous studies highlighting the antioxidant and anti-inflammatory properties of *N. sativa*, particularly through its active compound, thymoquinone (Hannan et al., 2021; Isaev et al., 2023). However, further research is needed to compare its efficacy with other that of other well-established antioxidants, such as vitamin C and polyphenols, which have also been reported to reduce oxidative stress in exercise settings (Torre et al., 2021).

Not all types of exercise induce the same levels of oxidative stress and inflammation. The magnitude of ROS production and inflammatory response depends on the intensity, duration, and type of exercise performed (Supruniuk et al., 2023). Some forms of exercise significantly increase oxidative stress and inflammation (Irawan et al., 2024). High-intensity exercises, such as HIIT, sprinting, and CrossFit, lead to increased oxygen consumption and mitochondrial activity, resulting in higher ROS production (Fernández-Lázaro et al., 2020). Endurance training, including marathons, cycling, and long-distance running, enhances oxidative metabolism and lipid peroxidation due to prolonged exercise duration (Wu et al., 2019). Additionally, eccentric and heavy resistance training, such as weightlifting and plyometric training, can cause muscle microdamage, triggering inflammatory responses and HMGB1 release (Goh & Behringer, 2018).

Malondialdehyde (MDA) is a well-established biomarker of oxidative stress and lipid peroxidation, which increases following intense physical activity. The results show that MDA levels were significantly lower in the *N. sativa* group than in the Placebo group at T1 and T2 ($p < 0.001$). This suggests that *N. sativa* supplementation may mitigate oxidative damage by

enhancing the body's natural antioxidant defense system. These findings align with previous studies indicating that *N. sativa* is rich in thymoquinone, a compound with potent antioxidant properties that can scavenge free radicals and reduce oxidative stress.

The significant Group $\times$ Time interaction effect ($F(2, 88) = 41.61, p < 0.001$; Table 5) indicates that MDA levels were differentially regulated over time between the *Nigella sativa* and placebo groups. Notably, the *N. sativa* group demonstrated a smaller increase in MDA immediately post-exercise (T1) and a faster reduction at T2, suggesting a potential protective effect against exercise-induced oxidative stress. This effect may be attributed to *N. sativa*'s ability to enhance endogenous antioxidant defenses, particularly through the upregulation of key enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), which act synergistically to neutralize reactive oxygen species (ROS) and prevent lipid peroxidation (Ratheesh et al., 2021).

High-mobility group box 1 (HMGB1) is a key pro-inflammatory mediator released in response to cellular stress and tissue damage. The results indicate that HMGB1 levels were significantly lower in the *N. sativa* group compared to Placebo at T1 and T2 ($p < 0.001$), demonstrating its anti-inflammatory potential. The observed reduction in HMGB1 levels suggests that *N. sativa* may suppress inflammation by modulating key inflammatory pathways, such as the NF- κ B signaling pathway, which plays a central role in cytokine production and immune response activation (Wang, 2022). Previous studies have also shown that thymoquinone inhibits pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β , which are closely linked to HMGB1 release (Alsousi & Igwe, 2018). However, further investigations are needed to confirm whether *N. sativa* has a direct inhibitory effect on NF- κ B activation in human skeletal muscle following exercise (Hannan et al., 2021).

Overall, the results of this study support the potential of *N. sativa* supplementation as a natural strategy to mitigate exercise-induced oxidative stress and inflammation. Given the increasing interest in plant-based recovery strategies, *N. sativa* may serve as an alternative to synthetic antioxidants, particularly for athletes seeking to optimize post-exercise recovery without compromising adaptive responses. Further exploration of its molecular mechanisms and long-term effects will be essential to establish its role in sports nutrition and recovery protocols fully.

Limitations

The results of this study provide strong evidence that *N. sativa* supplementation significantly reduces oxidative stress (MDA) and inflammation (HMGB1) following exercise. These effects are time-dependent, with the greatest benefits observed immediately after exercise and persisting for 24 hours. Given that exercise-induced ROS production and inflammation can impair recovery, *N. sativa* may serve as an effective natural supplement for post-exercise recovery, offering both antioxidant and anti-inflammatory protection. These findings suggest that *N. sativa* supplementation could be integrated into sports nutrition strategies as a natural and safe approach to reduce oxidative stress and inflammation, potentially enhancing recovery and optimizing athletic performance. Future studies should explore its long-term effects and molecular mechanisms to validate its potential applications in sports nutrition further.

CONCLUSION

The results of this study provide strong evidence that *N. sativa* supplementation significantly reduces oxidative stress (MDA) and inflammation (HMGB1) following exercise. These effects are time-dependent, with the greatest benefits observed immediately after exercise and persisting for 24 hours. Given that exercise-induced ROS production and inflammation can impair recovery, *N. sativa* may serve as an effective natural supplement for post-exercise recovery, offering both antioxidant and anti-inflammatory protection. These findings suggest that *N. sativa* supplementation could be integrated into sports nutrition strategies as a natural and safe approach to reduce oxidative stress and inflammation, potentially enhancing recovery and optimizing athletic performance. Future studies should explore its long-term effects and molecular mechanisms to validate its potential applications in sports nutrition further.

PRACTICAL IMPLICATIONS

The findings of this study have important practical implications for coaches, trainers, and sports nutritionists. The ability of *Nigella Sativa* seed extract to reduce oxidative stress and inflammation suggests its potential as a natural and safe supplement to enhance post-exercise recovery. This study specifically utilized standardized black seed (*Nigella Sativa* seed) extract rich in thymoquinone, which has been identified as the primary bioactive compound responsible for its antioxidant and anti-inflammatory effects. It is essential to note that not all parts of the *N. sativa* plant exhibit the same efficacy; current evidence suggests that the use of

the seeds, rather than the whole plant or oil preparations, yields more consistent therapeutic outcomes. By integrating standardized *N. sativa* seed extract into athletes' nutrition plans, recovery time may be improved, muscle damage minimized, and overall performance optimized. This could be particularly beneficial for athletes engaged in high-intensity or endurance training, where excessive ROS production and prolonged inflammation may hinder performance and adaptation. Future research should explore individualized dosing strategies, formulation types, and long-term effects across different athletic populations to further validate its role in sports recovery programs.

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Authors' Contribution

The study was conceived and designed by the first, third, and sixth authors. Data collection was carried out by the first, second, third, and fourth authors. Data analysis and interpretation were conducted by the first, second, fourth, and fifth authors. The manuscript was drafted and/or critically revised by the first, fifth, and sixth authors. Final approval of the version to be published was given by all six authors.

Declaration of Conflict Interest

Authors state that there is no conflict of the interest.

Ethics Statement

This study was approved by the Health Research Ethics Committee of the Faculty of Public Health, Universitas Airlangga (Ethical No: 104/EA/KEPK/2023). Individual consent forms were also collected from the participants.

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