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Effects of Nigella sativa Supplementation on Post-Exercise Inflammation and Muscle Damage in Recreationally Active Individuals

Rekreasyonel Olarak Aktif Bireylerde Nigella sativa (Çörek Otu) Takviyesinin Egzersiz Sonrası Enflamasyon ve Kas Hasarı Üzerindeki Etkileri

Roy Januardi IRAWAN[1]
[1]Universitas Negeri Surabaya, Faculty of Sports Science and Health, Sports Science Department, Surabaya, Indonesia

Mokhamad BAWONO[1]
[1]Universitas Negeri Surabaya, Faculty of Sports Science and Health, Sports Science Department, Surabaya, Indonesia

Dıta YULİASTRİD[1]
[1]Universitas Negeri Surabaya, Faculty of Sports Science and Health, Sports Science Department, Surabaya, Indonesia

Abdul Rohim TUALEKA[2]
[2]Universitas Airlangga, Faculty of Public Health, Department of Occupational Health and Safety, Surabaya, Indonesia

Putri Ayuni ALAYYANNUR[2]
[2]Universitas Airlangga, Faculty of Public Health, Department of Occupational Health and Safety, Surabaya, Indonesia

ABSTRACT

Exercise-induced muscle damage (EIMD) leads to muscle fiber disruption, inflammation, and elevated biomarkers such as interleukin-6 (IL-6) and creatine kinase (CK). Effective recovery strategies are crucial to mitigate inflammation and accelerate muscle repair. *Nigella sativa* (NS), rich in thymoquinone, possesses anti-inflammatory and antioxidant properties, but its role in post-exercise IL-6 and CK regulation remains unclear. This double-blind, placebo-controlled trial investigated the effects of NS supplementation on IL-6 and CK levels following high-intensity eccentric exercise in 40 recreationally active males. Participants received either NS (500 mg twice daily for 7 days pre-exercise) or a placebo. They performed an eccentric exercise protocol, with blood samples collected at baseline (T0), immediately post-exercise (T1), and 24 hours post-exercise (T2). IL-6 and CK were analyzed using ELISA and an automated biochemical analyzer, and data were processed using two-way repeated measures ANOVA. Post-exercise, IL-6 and CK levels rose significantly in both groups, indicating inflammation. However, the NS group showed markedly lower IL-6 and CK at T_1 and T_2 (p< .001), suggesting that NS supplementation attenuates inflammation and muscle damage after intense exercise**.** NS shows promise as a natural anti-inflammatory and muscle-protective agent, comparable to BCAAs, curcumin, and omega-3, though further research is required to clarify optimal dosing, long-term effects, and potential synergies.

Keywords: Nigella sativa, exercise-induced muscle damage, IL-6, creatine kinase, inflammation, eccentric exercise

ÖZ

Egzersize bağlı kas hasarı (EIMD), kas lifi bozulmasına, iltihaplanmaya ve interlökin-6 (IL-6) ve kreatin kinaz (CK) gibi biyobelirteçlerin yükselmesine yol açar. Etkili iyileşme stratejileri, iltihabı azaltmak ve kas onarımını hızlandırmak için büyük önem taşımaktadır. Timokinon açısından zengin olan *Nigella sativa (Çörek otu; NS)'nın anti-inflamatuar* ve antioksidan özelliklere sahip olduğu bilinmekle birlikte, egzersiz sonrası IL-6 ve CK düzenlemesindeki rolü belirsizliğini korumaktadır. Bu çift kör, plasebo kontrollü çalışma, 40 rekreasyonel olarak aktif erkek katılımcıda yüksek yoğunluklu eksantrik egzersiz sonrasında *Nigella sativa* (NS) takviyesinin IL-6 ve CK düzeyleri üzerindeki etkilerini araştırmıştır. Katılımcılara egzersiz öncesindeki 7 gün boyunca günde iki kez 500 mg NS veya plasebo verilmiştir. Katılımcılar eksantrik egzersiz protokolünü uygulamış ve kan örnekleri başlangıçta (T_0), egzersizden hemen sonra (T_1) ve egzersizden 24 saat sonra (T_2) alınmıştır. IL-6 ve CK düzeyleri, ELISA ve otomatik biyokimyasal analizör kullanılarak analiz edilmiş, veriler ise iki yönlü tekrarlayan ölçümler ANOVA yöntemiyle değerlendirilmiştir. Egzersiz sonrasında her iki grupta da IL-6 ve CK düzeyleri anlamlı şekilde artarak inflamatuar yanıtı göstermiştir. Ancak, NS grubunda T_1 ve T_2'de IL-6 ve CK düzeyleri belirgin olarak daha düşük bulunmuş (p<,001), bu da NS takviyesinin yoğun egzersiz sonrası inflamasyon ve kas hasarını azalttığını göstermektedir. NS, dallı zincirli amino asitler (BCAA), kurkumin ve omega-3'e benzer şekilde doğal bir antiinflamatuar ve kas koruyucu ajan olarak umut vadetmektedir. Ancak, optimal dozun, uzun vadeli etkilerin ve diğer toparlanma stratejileriyle olası sinerjilerin belirlenmesi için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Nigella sativa, egzersize bağlı kas hasarı, IL-6, kreatin kinaz, enflamasyon, eksantrik egzersiz

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Sorumlu Yazar/Corresponding author: Roy Januardi Irawan
E-mail: royjanuardi@unesa.ac.id
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Introduction

Regular physical activity is essential for maintaining overall health, enhancing muscular strength, and improving metabolic function (Smith et al., 2023). However, participation in high-intensity or unfamiliar exercise often induces exercise-induced muscle damage (EIMD), a physiological response characterized by microtears in muscle fibers, sarcomere disruption, and subsequent inflammatory processes (Tomalka, 2023; Wilke & Behringer, 2021). While EIMD is a natural component of muscle adaptation, it is commonly accompanied by delayed onset muscle soreness (DOMS), stiffness, and temporary declines in performance (Ali et al., 2023; Sulistyarto et al., 2022). If not managed properly, excessive or prolonged muscle damage can result in chronic inflammation, impaired muscle function, and an increased risk of injury (Irawan et al., 2021; Wiecha et al., 2024). These potential risks highlight the importance of identifying which groups are most vulnerable to EIMD and require special attention in terms of recovery strategies.

These concerns are particularly relevant for recreationally active individuals, a growing population that regularly engages in exercise for health, fitness, or leisure but is not professional or elite (Heckel et al., 2024). Unlike elite athletes, they often lack structured recovery protocols, making them more vulnerable to EIMD, inflammation, and DOMS when performing high-intensity or novel exercise routines (Philpott et al., 2023). Inadequate recovery in this group not only reduces performance and elevates injury risk but may also discourage long-term adherence to physical activity. Consequently, understanding and monitoring post-exercise responses in recreational populations is crucial, as it safeguards muscle function and promotes sustainable engagement in exercise (Bonilla et al., 2022). Investigating interventions such as Nigella sativa supplementation offers practical and accessible strategies to mitigate post-exercise inflammation and muscle damage, supporting both performance and long-term health.

Among the inflammatory mediators, interleukin-6 (IL-6) shows the most pronounced elevation following exercise, acting as both a pro- and anti-inflammatory cytokine (Beba et al., 2022; Nara & Watanabe, 2021). Other cytokines affected by exercise include tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-10 (IL-10), which collectively regulate inflammation and muscle repair (Aguiar et al., 2020). Creatine kinase (CK) is a well-established biomarker reflecting structural muscle damage, providing complementary information on muscle integrity (Huang et al., 2021; Wolska et al., 2023). Taken together, IL-6 and CK serve as reliable indicators of post-exercise inflammation and tissue damage, thereby allowing a comprehensive evaluation of recovery interventions.

Given the increasing participation in recreational and competitive sports worldwide (Tahira, 2022; Westerbeek & Eime, 2021), effective recovery strategies are crucial to maintaining performance and preventing long-term muscle dysfunction. Current post-exercise recovery interventions often rely on synthetic anti-inflammatory drugs, such as ibuprofen and naproxen, to alleviate muscle soreness and reduce inflammation (Pham & Spaniol, 2024; Sohail et al., 2023), however, their prolonged or repeated use may be associated with gastrointestinal, renal, and cardiovascular adverse effects (Bateman et al., 2023; Sohail et al., 2023). Therefore, the exploration of natural alternatives has become increasingly important, with Nigella sativa (NS) emerging as a promising option due to its demonstrated anti-inflammatory and antioxidant properties (Sadeghi et al., 2023; Sarkar et al., 2021).

Previous research has explored various strategies to mitigate EIMD, including nutritional interventions, active recovery, cryotherapy (Azevedo et al., 2022), and anti-inflammatory supplementation (Irawan et al., 2022). Nutrients such as branched-chain amino acids (BCAAs), omega-3 fatty acids, polyphenols, curcumin, vitamin D, and creatine have demonstrated beneficial effects in reducing muscle damage and inflammation (de Salazar et al., 2020; Kruk et al., 2022; Rahmat et al., 2021; Spoelder et al., 2023). Despite these advances, studies specifically investigating plant-based interventions like NS remain limited, and only a few have examined its impact on IL-6 and CK levels in recreationally active populations.

The present study aims to investigate the effects of NS supplementation on IL-6 and CK levels following a high-intensity eccentric exercise protocol in recreationally active university students. This study is original in focusing on the combined assessment of these biomarkers in this population, providing a comprehensive evaluation of NS as a natural recovery strategy. By comparing NS supplementation to a placebo, the research seeks to clarify its potential to attenuate post-exercise inflammation and muscle damage, thereby contributing to evidence-based recommendations for natural post-exercise recovery and extending insights beyond previous studies on general health benefits or elite athletes.

Methods

Study Design

This study employs a randomized controlled trial (RCT) design to investigate the effects of NS supplementation on IL-6 and CK levels following EIMD. Participants will be randomly assigned to either the NS supplementation group or the placebo group using a double-blind, placebo-controlled design. The total duration of the study, including randomization, supplementation, exercise intervention, and follow-up measurements, will be approximately 10–12 days, ensuring sufficient time for pre-exercise supplementation, intervention, and post-exercise assessments.

Participants

A total of 40 recreationally active male university students (aged 18–21 years) from the Department of Sport Science, Universitas Negeri Surabaya, will be recruited using purposive sampling. Participants eligible for this study were male university students majoring in physical education who engage in recreational training activities, such as resistance exercises, cardiovascular workouts, and general fitness routines, 3–5 times per week for at least six months, and have no history of chronic inflammatory diseases or musculoskeletal disorders. These participants are not competitive athletes but maintain regular training for health, fitness, and skill development. The age range of 18–21 years was chosen to ensure a relatively homogeneous sample with similar physiological responses to exercise. Individuals currently using anti-inflammatory medications or supplements, those with a history of cardiovascular, metabolic, or neuromuscular diseases, or those with allergies to NS or its components will be excluded.

Participants will be randomly assigned to either the NS supplementation group (n=20) or the placebo group (n=20) using a double-blind, placebo-controlled design. The sample size was determined using G*Power software with a power analysis based on prior studies examining nutritional interventions for muscle damage. A power (1-β) of 0.80, a significance level (α) of 0.05, and an effect size (Cohen's d) of 0.8 were used to calculate the required sample size. The analysis indicated that a minimum of 34 participants (17 per group) is needed to detect a statistically significant difference. To account for potential dropouts, the sample size was increased to 40 participants. This study was approved by the Health Research Ethics Committee, Faculty of Public Health, Airlangga University (No. 104/EA/KEPK/ / 10 May 2023). Written informed consent was obtained from all participants after they were informed about the study procedures, potential risks, and benefits. The study was conducted in accordance with the Declaration of Helsinki.

Exercise Protocol

To induce exercise-induced muscle damage (EIMD), this study utilized the (Miyama and Nosaka, 2004) eccentric exercise protocol, a well-established method for generating significant muscle fiber disruption and inflammatory responses. Participants performed a series of eccentric-only leg extensions, targeting the quadriceps muscle group, using a resistance equivalent to 120% of their one-repetition maximum (1RM). The exercise consisted of 12 sets of 5 repetitions, with participants solely resisting the downward phase of the movement, while the concentric phase was assisted by the researchers. This high-intensity eccentric loading was designed to cause microtears in the muscle fibers, sarcomere disruption, and an acute inflammatory response, mimicking the muscle damage experienced during strenuous physical activities such as downhill running or plyometric exercises. The protocol was selected due to its reproducibility and effectiveness in elevating key biomarkers of muscle damage, particularly creatine kinase (CK) and interleukin-6 (IL-6), within 24 hours post-exercise. Blood samples were collected at baseline (T0), immediately post-exercise (T1), and 24 hours post-exercise (T2) to assess the potential of Nigella sativa supplementation in mitigating muscle damage in recreationally active individuals.

Supplementation Protocol

The intervention group will receive 500 mg of NS extract in the form of soft gel capsules twice daily for seven days prior to exercise. The placebo group will receive identical capsules containing an inert substance. Supplementation adherence will be monitored through participant logs. Participants will be instructed to avoid any additional anti-inflammatory supplements or medications during the study period. The 500 mg dosage was chosen based on previous studies showing its efficacy in

reducing oxidative stress and inflammation in physically active individuals (Benazzouz-Smail et al., 2023).

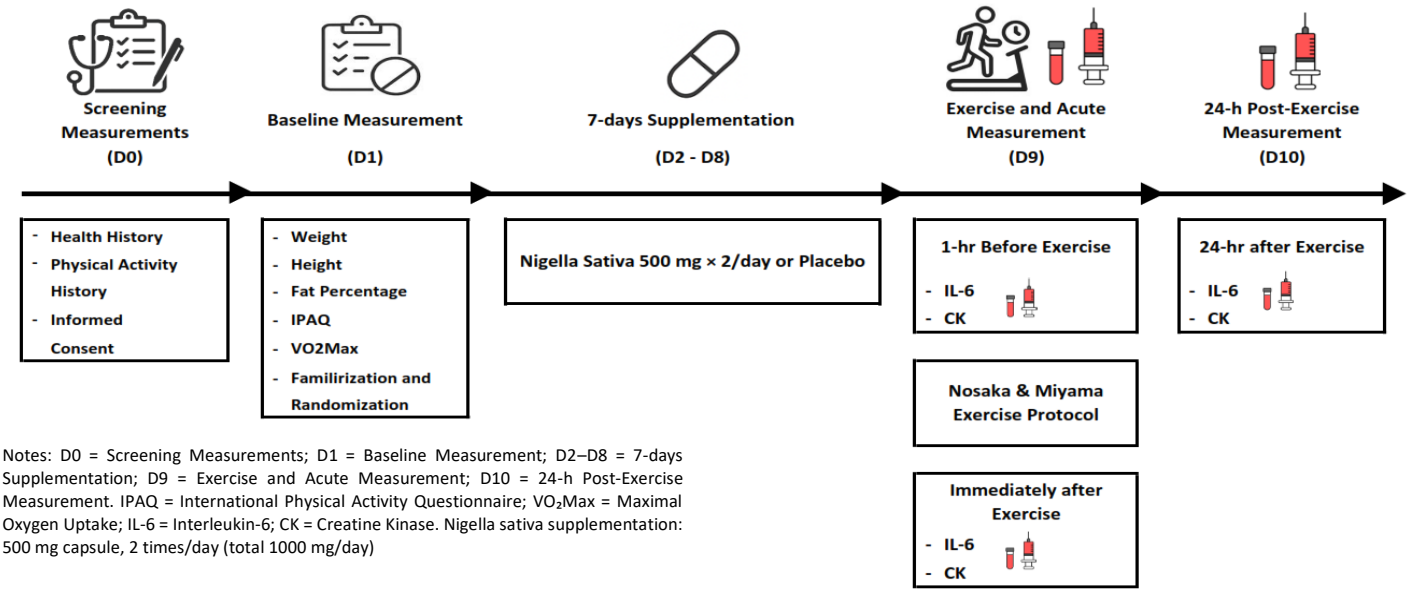
The duration of 7 days for pre-exercise supplementation was selected based on existing research on natural anti-inflammatory and antioxidant supplementation (Sifuentes-Franco et al., 2022). Studies have shown that a minimum of one week is required for bioactive compounds like thymoquinone in Nigella Sativa to reach optimal levels in circulation and exert protective effects against oxidative stress and inflammation. This timeframe ensures that the participants experience the full potential of NS in reducing IL-6 and CK levels post-exercise while maintaining practical feasibility for adherence.

Outcome measure

Blood samples will be collected from the cubital vein using a sterile needle at three time points: before exercise (T0), immediately after exercise (T1), and 24 hours post-exercise (T2). Approximately 5 mL of blood will be drawn at each time point. To analyze plasma IL-6 levels, blood samples will be placed in EDTA tubes and immediately centrifuged at 3000 rpm for 15 minutes to separate plasma. The obtained plasma will be stored at -20°C until further analysis. Meanwhile, to measure serum CK, blood samples will be collected in plain serum tubes, allowed to clot at room temperature for 30 minutes, and then centrifuged at 3000 rpm for 15 minutes to separate serum. The separated serum will also be stored at -20°C until biochemical analysis. Plasma IL-6 levels will be quantified using an enzyme-linked immunosorbent assay (ELISA) kit (Abexxa), according to the manufacturer's instructions. Absorbance will be measured using a microplate reader at the specified wavelength, and results will be expressed in pg/mL. Meanwhile, serum CK levels will be analysed using an automated biochemical analyse based on an enzymatic colorimetric method. CK activity will be determined through the conversion of creatine phosphate and ADP into creatine and ATP, with results reported in U/L. To ensure data validity, samples will be visually inspected for haemolysis before analysis. Haemolyzed samples will be excluded to prevent measurement bias. All procedures will be conducted by trained medical personnel under aseptic conditions to minimize the risk of contamination or measurement errors. Laboratory analyses will be carried out at the Sports Science Laboratory, Universitas Negeri Surabaya, and the Faculty of Public Health Laboratory, Airlangga University.

A summary of the study design is presented in Figure 1.

Figure 1.
Study Design



Notes: D0 = Screening Measurements; D1 = Baseline Measurement; D2–D8 = 7-days Supplementation; D9 = Exercise and Acute Measurement; D10 = 24-h Post-Exercise Measurement. IPAQ = International Physical Activity Questionnaire; VO_2Max = Maximal Oxygen Uptake; IL-6 = Interleukin-6; CK = Creatine Kinase. Nigella sativa supplementation: 500 mg capsule, 2 times/day (total 1000 mg/day)

Statistical Analysis

All statistical analyses will be performed using SPSS version 23 (IBM SPSS Corp., Armonk, NY, USA). The Shapiro-Wilk test

will assess data normality. Descriptive statistics will be presented as mean ± standard deviation (SD). A two-way repeated-measures ANOVA will analyze differences between groups (NS vs. placebo) and across time points (T0, T1, and T2). If a significant interaction is found, Bonferroni post-hoc tests will be conducted for pairwise comparisons. Effect sizes (partial eta squared, η^2p) will be reported to indicate the magnitude of differences. A *p*-value < .05 will be considered statistically significant for all analyses.

Results

Respondent Characeristic

All statistical analyses will be performed using SPSS version 23. The Shapiro-Wilk test will assess data normality. Descriptive statistics will be presented as mean ± standard deviation (SD). A two-way repeated-measures ANOVA will analyze differences between groups (NS vs. placebo) and across time points (T0, T1, and T2). If a significant interaction is found, Bonferroni post-hoc tests will be conducted for pairwise comparisons. A *p*-value < .05 will be considered statistically significant for all analyses.

The characteristics of the respondents in this study include age, height, body weight, body mass index (BMI), body fat percentage, and lean body mass (LBM). A total of 40 participants were divided into two groups: the Nigella sativa group and the placebo group, with 20 participants in each. Descriptive statistical analysis was conducted to summarize the distribution of baseline characteristics in both groups.

Other characteristics, such as body weight, body fat percentage, and lean body mass, also showed similar distributions between the two groups. This balance in baseline characteristics suggests that the randomization process was successful in achieving an even distribution between the intervention and control groups, minimizing potential bias in analyzing the effects of Nigella sativa supplementation on post-exercise IL-6 and CK levels.

The data presented in Table 1 indicate that both groups had similar baseline characteristics, ensuring that any differences observed in subsequent analyses are more likely attributable to the effects of Nigella sativa supplementation rather than pre-existing variations.

Table 1.
Respondent Characteristic

Variable	NS Group Mean (±SD)	Placebo Group Mean (±SD)	*p*
Age (years)	19.60 ± 0.99	20.15 ± 0.81	.681
Height (cm)	168.40 ± 3.49	167.35 ± 3.69	.926
Weight (kg)	60.45 ± 4.14	61.50 ± 5.02	.788
BMI	21.31 ± 1.23	21.95 ± 1.59	.648
Fat percentage (%)	19.01 ± 0.01	18.73 ± 0.51	.825
IPAQ (MET)	1104.33 ± 222.56	1166.68 ± 217.02	.572
VO_2max (mL/kg·min)	34.33 ± 5.34	35.65 ± 6.03	.353
Lean body mass (kg)	48.06 ± 3.07	49.73 ± 4.22	.598

Note: Data are presented as mean ± standard deviation. *NS* = *Nigella sativa*; *BMI* = body mass index; *IPAQ* = International Physical Activity Questionnaire; *MET* = metabolic equivalent of task; *VO_2max* = maximal oxygen uptake. No significant differences were observed between groups at baseline (*p*>.05).

These baseline characteristics indicate that both groups were well-matched, ensuring fair comparisons in subsequent analyses.

Normality and Homogeinity Test Result

The results of the normality test indicated that plasma IL-6 and creatine kinase (CK) levels in both the Nigella sativa (NS) and placebo groups were normally distributed across all time points (T0, T1, and T2). The Shapiro-Wilk test yielded p-values ranging from 0.282 to 0.848 for IL-6 and from 0.361 to 0.944 for CK, all exceeding 0.05. These findings confirm that the data did not deviate significantly from a normal distribution.

Since the assumption of normality was met, the next step was to assess the homogeneity of variances. Levene's test was therefore conducted to determine whether equal variances were present between groups, ensuring the suitability of parametric tests such as ANOVA for subsequent analyses.

Table 2.
Homogeneity test result

Variable	T0 NS – Placebo Sig.	T1 NS – Placebo Sig.	T2 NS – Placebo Sig.
IL-6	0.758	0.011	< 0.001
CK	0.757	< 0.001	< 0.001

Note. *NS* = *Nigella sativa*; *T0* = before exercise; *T1* = immediately post-exercise; *T2* = 24 hours post-exercise; *IL-6* = interleukin-6; *CK* = creatine kinase. Values represent between-group comparisons (NS vs. placebo) at each time point

The homogeneity test was conducted using Levene's test to determine whether the variance between groups for each variable was homogeneous. The results are presented in Table 3, showing the significance values (Sig.) at different time points (T0, T1, and T2) for IL-6 and Creatine Kinase (CK).

These results suggest that before the intervention (T0), the variances between the NS and Placebo groups were homogeneous, allowing the use of an Independent Sample T-Test assuming equal variances. However, after the intervention (T1 and T2), the variances became non-homogeneous, requiring the use of Welch's t-test correction to ensure the validity of group comparisons.

Plasma IL-6 Assessment Result

IL-6 Is a pro-inflammatory and anti-inflammatory cytokine that plays a crucial role in the body's response to exercise-induced muscle injury. Plasma IL-6 was assessed at 1 hour before, immediately after and 24-hours post-exercise. Descriptive statistics of plasma IL-6 levels are presented in Table 3. At baseline (T0), the mean plasma IL-6 concentrations were similar between the NS (4.33 ± 0.96 pg/mL) and Placebo groups (4.23 ± 0.97 pg/mL). Following exercise (T1), IL-6 levels increased in both groups, with higher values observed in the Placebo group (7.21 ± 1.21 pg/mL) compared to the NS group (6.32 ± 0.90 pg/mL). At 24 hours post-exercise (T2), IL-6 concentrations declined in both groups but remained elevated relative to baseline, with the Placebo group showing higher values (5.99 ± 1.31 pg/mL) than the NS group (4.52 ± 0.87 pg/mL).

Table 3.
IL-6 plasma level

Group	T0 before Mean ± SD (pg/mL)	T1 post Mean ± SD (pg/mL)	T2 post Mean ± SD (pg/mL)
NS	4.33 ± 0.96	6.32 ± 0.90	4.52 ± 0.87
Placebo	4.23 ± 0.97	7.21 ± 1.21	5.99 ± 1.31

Notes. *T0* = before exercise; *T1* = immediately post-exercise; *T2* = 24 hours post-exercise; *NS* = *Nigella sativa*. Data are presented as mean ± standard deviation. Statistical comparisons and effect sizes are reported in Table 4.

Table 4.
Results of repeated-measures ANOVA for plasma IL-6

Source	df	F	p	Partial Eta Squared
Time	2,76	363.55	<0.001	0.905 (very large)
Time × Group	2,76	36.21	<0.001	0.488 (large)
Linear (Time)	1,38	80.01	<0.001	0.678 (large)

Table 4.
Results of repeated-measures ANOVA for plasma IL-6

Source	df	F	p	Partial Eta Squared
Quadratic (Time)	1,38	1000.64	<0.001	0.963 (very large)
Linear (Time × Group)	1,38	51.07	<0.001	0.573 (large)
Quadratic (Time × Group)	1,38	2.81	0.102	0.069 (small)

Notes. *df* = degrees of freedom; *F* = F-ratio; *p* = probability value; Partial η^2 = partial eta squared (effect size estimate). Interpretation of effect size: small ($\eta^2_p \approx 0.01$), medium ($\eta^2_p \approx 0.06$), large ($\eta^2_p \approx 0.14$).

A repeated-measures ANOVA indicated a significant main effect of time on plasma IL-6 ($F(2,76)=363.55$, $p<.001$, $\eta^2p=.905$), representing a very large effect size. A significant time × group interaction was also detected ($F(2,76)=36.21$, $p<.001$, $\eta^2p=.488$), demonstrating differential IL-6 responses between groups across time points. Planned contrasts revealed a significant linear trend over time ($F(1,38)=80.01$, $p<.001$, $\eta^2p=.678$) and a significant quadratic trend ($F(1,38)=1000.64$, $p<.001$, $\eta^2p=.963$). The interaction between time and group was significant for the linear component ($F(1,38)=51.07$, $p<.001$, $\eta^2p=.573$), but not for the quadratic component ($F(1,38)=2.81$, $p=.102$, $\eta^2p=.069$).

Serum CK Assessment Result

Creatine kinase (CK) is a well-established biomarker of muscle damage that reflects sarcolemmal disruption and cellular leakage following strenuous exercise. Serum CK was assessed at 1 hour before, immediately after, and 24 hours post-exercise. Descriptive statistics of serum CK levels are presented in Table 5. At baseline (T0), the mean serum CK concentrations were comparable between the NS (117.68 ± 14.40 U/L) and Placebo groups (116.26 ± 0.97 U/L). Following exercise (T1), CK levels markedly increased in both groups, with higher values observed in the Placebo group (197.15 ± 17.56 U/L) compared to the NS group (235.47 ± 30.64). At 24 hours post-exercise (T2), CK concentrations remained elevated relative to baseline in both groups, but the Placebo group demonstrated persistently higher values (147.50 ± 19.68 U/L) compared to the NS group (204.81 ± 32.34 U/L).

Table 5.
CK serum level

Group	T0 before Mean ± SD (U/L)	T1 post Mean ± SD (U/L)	T2 post Mean ± SD (U/L)
NS	117.68 ± 14.40	197.15 ± 17.56	147.50 ± 19.68
Placebo	116.26 ± 0.97	235.47 ± 30.64	204.81 ± 32.34

Notes. *T0* = before exercise; *T1* = immediately post-exercise; *T2* = 24 hours post-exercise; *NS* = *Nigella sativa*; *SD* = standard deviation; *U/L* = units per liter. Data are presented as mean ± SD. Statistical comparisons and effect sizes are reported in Table 6.

Table 6.
Results of repeated-measures ANOVA for serum CK

Source	df	F	*p*	Partial Eta Squared
Time	2,76	457.76	<.001	0.923 (very large)
Time × Group	2,76	41.16	<.001	0.520 (large)
Linear (Time)	1,38	227.22	<.001	0.857 (very large)

Table 6.
Results of repeated-measures ANOVA for serum CK

Source	df	F	*p*	Partial Eta Squared
Quadratic (Time)	1,38	1012.71	<.001	0.964 (very large)
Linear (Time × Group)	1,38	55.93	<.001	0.595 (large)
Quadratic (Time × Group)	1,38	5.61	.023	0.129 (small-medium)

Notes. *df* = degrees of freedom; *F* = F-ratio; *p* = probability value; Partial η^2_p = partial eta squared (effect size estimate). Interpretation of effect size: small ($\eta^2_p \approx 0.01$), medium ($\eta^2_p \approx 0.06$), large ($\eta^2_p \approx 0.14$).

A repeated-measures ANOVA indicated a significant main effect of time on serum CK ($F(2,76)=457.76$, $p<.001$, $\eta^2p=.923$), representing a very large effect size. A significant time × group interaction was also detected ($F(2,76)=41.16$, $p<.001$, $\eta^2p=.520$), demonstrating differential CK responses between groups across time points. Planned contrasts revealed a significant linear trend over time ($F(1,38)=227.22$, $p<.001$, $\eta^2p=.857$) and a significant quadratic trend ($F(1,38)=1012.71$, $p<.001$, $\eta^2p=.964$). The interaction between time and group was significant for the linear component ($F(1,38)=55.93$, $p<.001$, $\eta^2p=.595$) and also for the quadratic component ($F(1,38)=5.61$, $p=.023$, $\eta^2p=.129$).

Discussion

This study aimed to investigate the effects of Nigella sativa (NS) supplementation on IL-6 and CK levels following exercise-induced muscle damage (EIMD) in recreationally active individuals. The results demonstrated that NS supplementation significantly reduced IL-6 and CK levels post-exercise compared to the placebo group, suggesting that NS may have anti-inflammatory and muscle-protective properties.

Nutritional intervention studies play a crucial role in optimizing exercise recovery, muscle repair, and inflammation regulation (Garthe & Maughan, 2018). These studies examine the effects of various dietary strategies, supplements, or bioactive compounds in mitigating the physiological stress induced by exercise (Coqueiro et al., 2019). The primary goal of nutritional interventions is to enhance performance adaptation, accelerate muscle recovery, and reduce muscle damage, thereby supporting both athletic performance and long-term health (Sánchez Díaz et al., 2022). Several nutritional strategies have been explored to aid in post-exercise muscle recovery and inflammation control. Protein and amino acids, particularly branched-chain amino acids (BCAAs) (Şentürk & Göbel, 2022) and whey protein (Spoelder et al., 2023), have been shown to reduce post-exercise muscle soreness and CK levels, promoting faster recovery. Omega-3 fatty acids are also widely studied for their anti-inflammatory properties (O'Connor et al., 2022), as they help regulate cytokine release and cell membrane integrity, thereby reducing IL-6 levels post-exercise. Additionally, polyphenols such as curcumin and resveratrol have been found to possess antioxidant and anti-inflammatory effects (Ayubi et al., 2024), minimizing oxidative stress and muscle damage. Another well-known intervention is creatine supplementation (Yang et al., 2022), which plays a crucial role in energy metabolism and has been found to reduce muscle inflammation and improve recovery following high-intensity resistance training.

Despite the effectiveness of these strategies, interest in plant-based nutritional interventions continues to grow, particularly those with antioxidant and anti-inflammatory properties. NS is one such natural compound that has demonstrated potential benefits in reducing muscle inflammation and oxidative stress (Hannan et al., 2021; Ratheesh et al., 2021). In this study, both IL-6 and CK levels increased significantly post-exercise (T1) in both groups, confirming that the exercise protocol effectively induced muscle damage and inflammation. However, IL-6 and CK levels were significantly lower in the NS group at T1 and T2, suggesting that NS supplementation may mitigate inflammation and muscle damage, promoting faster recovery.

Exercise-induced muscle damage is characterized by muscle fibre microtears, sarcomere disruption, and oxidative stress, leading to an inflammatory response (Wilke & Behringer, 2021). Two key biomarkers of this response are interleukin-6 (IL-6) and creatine kinase (CK), which play critical roles in inflammation and muscle damage assessment, respectively (Sánchez Díaz et al., 2022). IL-6 is produced by muscle fibers, macrophages, and neutrophils in response to exercise-induced tissue damage and metabolic stress (Irawan et al., 2022). It serves a dual role, acting as a pro-inflammatory mediator immediately post-exercise and transitioning into an anti-inflammatory regulator during the later recovery phase (Nara & Watanabe, 2021). IL-6 levels typically peak within 1–2 hours post-exercise, aiding in immune response activation and muscle regeneration (Lin et

al., 2021; Wadley et al., 2019). Meanwhile, CK is an intracellular enzyme that leaks into the bloodstream when muscle membrane integrity is compromised due to mechanical stress (Bontemps et al., 2020; Spoelder et al., 2023). Eccentric exercise significantly increases CK levels, with a peak occurring 24–72 hours post-exercise as muscle damage and repair processes continues (Chang et al., 2021).

The significant increase in IL-6 at T1 in both groups confirms that intense exercise triggers a systemic inflammatory response. However, IL-6 levels were significantly lower in the NS group at T1 and T2, indicating that NS supplementation may attenuate exercise-induced inflammation and accelerate recovery. The significant attenuation of IL-6 in the NS group confirms its anti-inflammatory potential, suggesting that NS may help modulate post-exercise inflammation, suppress excessive cytokine release, and accelerate the recovery process. This aligns with previous studies highlighting the ability of thymoquinone, the main bioactive compound in NS, to inhibit pro-inflammatory pathways and oxidative stress.

Thymoquinone exerts its anti-inflammatory effects primarily through the inhibition of the NF-κB signaling pathway, a key regulator of inflammatory responses (Mostafa et al., 2020). During exercise-induced muscle damage, NF-κB is activated by oxidative stress and inflammatory mediators (El Assar et al., 2022), leading to the transcription of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β (Ayubi et al., 2024). Thymoquinone prevents NF-κB activation by stabilizing IκB-α, its inhibitory protein, thereby reducing the excessive release of pro-inflammatory cytokines (Mostafa et al., 2020). Furthermore, thymoquinone interacts with the MAPK signalling pathway, particularly by inhibiting p38 MAPK phosphorylation, which plays a crucial role in IL-6 gene expression (Sadeghi et al., 2023). By suppressing both NF-κB and p38 MAPK activation, thymoquinone effectively reduces IL-6 production, thus limiting excessive inflammation and promoting a more controlled recovery response.

In addition to its role in inhibiting inflammatory signalling, thymoquinone also enhances the resolution of inflammation by upregulating IL-10, a key anti-inflammatory cytokine (Hussein et al., 2021). IL-10 acts as a counter-regulatory mechanism, preventing prolonged inflammation by inhibiting the synthesis of IL-6 and TNF-α (Saxton et al., 2021). Moreover, thymoquinone exhibits potent antioxidant properties, reducing the accumulation of reactive oxygen species (ROS) that exacerbate muscle damage and prolong inflammation (Raut et al., 2021). By limiting oxidative stress and promoting IL-10 release, NS supplementation may help balance the inflammatory response, ensuring a timely resolution of inflammation without compromising the body's natural recovery mechanisms.

Similarly, CK levels significantly increased post-exercise (T1) in both groups, confirming the expected muscle damage from high-intensity eccentric exercise. However, CK levels in the NS group were significantly lower than in the placebo group at both T1 and T2, suggesting that NS supplementation may protect muscle integrity and accelerate recovery. The observed reduction in CK aligns with findings from previous studies, which reported that NS supplementation reduced muscle enzyme leakage and oxidative stress in physically active individuals (Jangjo-Borazjani et al., 2023). The antioxidant and anti-inflammatory mechanisms of NS may contribute to stabilizing muscle membranes, thus reducing CK release into the bloodstream. When compared to branched-chain amino acids (BCAAs) and polyphenols, NS appears to be a promising alternative for muscle recovery. While BCAAs are known for their role in muscle protein synthesis(Greer et al., 2007), NS may offer additional benefits by reducing oxidative stress and inflammatory damage (Bhavikatti et al., 2024). Future research should explore the synergistic effects of NS with other well-established recovery strategies to optimize post-exercise muscle repair.

The results of this study suggest that NS supplementation may serve as a natural and effective strategy to mitigate inflammation and muscle damage following intense exercise. Given that many current recovery interventions rely on synthetic anti-inflammatory drugs, NS presents a promising alternative with fewer potential side effects. However, several limitations must be acknowledged. This study focused on short-term effects (24 hours post-exercise), and future research should examine the long-term impact of NS supplementation on muscle recovery. Additionally, only IL-6 and CK were analyzed as markers of inflammation and muscle damage. Future studies should explore additional biomarkers such as TNF-α, IL-10, lactate dehydrogenase (LDH), and oxidative stress markers to provide a more comprehensive understanding of NS's effects. Furthermore, the optimal dosage and timing of NS supplementation remain unclear, and further investigations are needed to determine whether higher doses or prolonged supplementation enhance recovery outcomes.

In conclusion, Nigella sativa supplementation significantly reduced post-exercise IL-6 and CK levels, suggesting potential anti-inflammatory and muscle-protective effects. These findings confirm that NS reduces exercise-induced inflammation and muscle damage, enhancing recovery in recreationally active individuals. Given its natural bioactive properties, NS may serve as a viable alternative to conventional recovery strategies. Further research is warranted to explore its long-term effects, optimal dosage, and potential synergy with other recovery interventions.

Conclussion and Recommendation

The findings of this study demonstrate that Nigella sativa (NS) supplementation significantly reduced post-exercise IL-6 and CK levels, suggesting its potential anti-inflammatory and muscle-protective effects in response to exercise-induced muscle damage (EIMD). The significant attenuation of IL-6 in the NS group indicates that NS may help modulate the inflammatory response, thereby promoting faster recovery. Similarly, the lower CK levels observed in the NS group suggest that NS supplementation may contribute to minimizing muscle fibre damage and accelerating muscle repair. These results support the hypothesis that NS can serve as a natural and effective intervention for enhancing post-exercise recovery in recreationally active individuals. Given the increasing reliance on synthetic anti-inflammatory drugs and commercial recovery supplements, NS presents a promising alternative due to its natural bioactive properties, antioxidant capacity, and safety profile.

Despite these promising findings, further research is needed to establish the optimal dosage, supplementation duration, and long-term effects of NS on exercise recovery. This study focused on short-term responses (24 hours post-exercise), and future studies should investigate the prolonged impact of NS on muscle recovery and performance adaptation over several days or weeks. Additionally, while IL-6 and CK were used as primary biomarkers in this study, subsequent research should explore other indicators of inflammation and muscle damage, such as TNF-α, IL-10, lactate dehydrogenase (LDH), and oxidative stress markers, to provide a more comprehensive understanding of NS's physiological effects. Future investigations should also compare NS supplementation directly with other well-established recovery strategies, such as BCAAs, curcumin, and omega-3 fatty acids, to determine its relative effectiveness in reducing muscle soreness, inflammation, and enhancing functional recovery.

Practical applications of NS supplementation should be further explored in different athletic populations, training regimens, and sports disciplines to assess its effectiveness across various exercise modalities. Additionally, controlled clinical trials with larger sample sizes and diverse subject demographics will be essential to confirm these findings and strengthen the evidence supporting NS as a reliable recovery aid. Given its potential anti-inflammatory and muscle-repair properties, NS supplementation may offer a safe, natural, and accessible recovery strategy for athletes and physically active individuals seeking to optimize their post-exercise recovery and overall performance.

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