ЗДОРОВ'Я ЛЮДИНИ, ФІТНЕС І РЕКРЕАЦІЯ, ФІЗИЧНЕ ВИХОВАННЯ РІЗНИХ ГРУП НАСЕЛЕННЯ

PHYTOCHEMICAL COMPOUNDS OF SEA CUCUMBER CONSUMED AFTER EXERCISE PROVEN TO SIGNIFICANTLY LOWER NF-KB LEVELS

ФІТОХІМІЧНІ СПОЛУКИ МОРСЬКОГО ОГІРКА, ЯКИЙ ВЖИВАЄТЬСЯ ПІСЛЯ ВПРАВ, ЗНАЧНО ЗНИЖУЮТЬ РІВЕНЬ NF-KB

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Abstracts

Purpose. The aim of this study was to analyze the effects of post-exercise sea cucumber supplementation on NF-kB levels as a biomarker of inflammation.

Material. An experimental study with a pre-test and post-test group design was conducted by comparing the placebo group (K1) with the treatment group (K2) which was given a 500 mg dose of sea cucumber supplement. A total of eighteen healthy men participated in this study. The method of examining NF-kB levels uses ELISA (Enzyme-linked immunosorbent assay).

Results. The characteristics of the research subjects were age, height, weight, BMI, and blood pressure (systolic and diastolic). The results of the t-test of the characteristics of the research subjects showed that there was no significant difference between K1 and K2 ($p \geq 0.05$). Furthermore, the results of the study reported that group K1 given placebo after exercise could not significantly reduce NF-kB levels ($p > 0.05$). Group K2 given sea cucumber supplementation after exercise could significantly reduce NF-kB levels (*$p < 0.05$). The phenolic and polyphenol content in sea cucumber supplementation has anti-inflammatory properties that positively impact reducing NF-kB levels after exercise. In addition, peptides in sea cucumbers function as reducing agents that can protect cells from increased NF-κB signaling, phosphoinositide 3-kinase or Akt signaling pathways, and mitogen-activated protein kinase. Decreased NF-kB levels have the potential to reduce proinflammatory cytokines such as TNF-a which are triggers of delayed onset muscle soreness after exercise.

Conclusions. It can be concluded that sea cucumber supplementation with a dose of 500 mg given after 24 hours of physical session can reduce NF-kB levels. In people who exercise regularly, sea cucumber supplementation is highly recommended as an additional supplement to suppress inflammation after exercise.

Key words: sea cucumber, exercise, inflammation, NF-kB.

Мета цього дослідження – проаналізувати вплив вживання морського огірка після фізичного навантаження на рівень NF-kB як біомаркера запалення.

Матеріал. Було проведено експериментальне дослідження з до– та післятестовим груповим дизайном, в якому порівнювали групу плацебо (К1) з групою лікування (К2), яка отримувала 500 мг добавки з морського огірка. У дослідженні взяли участь вісімнадцять здорових чоловіків. Для дослідження рівня NF-kB використовували метод ІФА (імуноферментний аналіз).

Результати. Характеристиками досліджуваних були вік, зріст, вага, ІМТ, артеріальний тиск (систолічний та діастолічний). Результати t-тесту характеристик обстежуваних показали, що достовірної різниці між К1 та К2 не було (p≥0,05). Крім того, результати дослідження показали, що група К1, яка отримувала плацебо після фізичного навантаження, не змогла суттєво знизити рівень NF-kB (p>0,05). У групі К2, яка приймала морські огірки після фізичного навантаження, рівень NF-kB значно знизився (*p<0,05). Вміст фенолів та поліфенолів у добавці з морських огірків має протизапальні властивості, які позитивно впливають на зниження рівня NF-kB після тренування. Крім того, пептиди в морських огірках функціонують як відновлювальні агенти, які можуть захищати клітини від підвищеної сигналізації NF-κB, фосфоінозитид-3-кінази або Akt-сигнальних шляхів, а також протеїнкінази, що активується мітогеном. Зниження рівня NF-kB має потенціал для зменшення прозапальних цитокінів, таких як ФНП-а, які є тригерами болю в м'язах після фізичних навантажень, що виникають із запізненням.

Висновки. Можна зробити висновок, що вживання морського огірка в дозі 500 мг через 24 години після фізичного навантаження може знизити рівень NF-kB. Людям, які регулярно займаються спортом, настійно рекомендується вживати морський огірок як додаткову добавку для пригнічення запалення після фізичних навантажень.

Ключові слова: морський огірок, фізичні вправи, запалення, NF-kB.

Introduction. An unpleasant emotional and sensory experience, pain serves vital physiological purposes by protecting internal organs from harmful stimulation [44]. Pain intensity is a serious health issue in the world, impacting 350 million individuals globally, and its prevalence continues to increase throughout the years [25]. Pain is part of the body's function to protect tissues from harmful stimuli. However, prolonged and severe pain will have a significant effect on health and develop into an unavoidable social issue [10]. The immune, sensory, and neurological systems' unique biochemical response to infection, tissue damage, and discomfort is inflammation [40]. The primary causes of inflammation-induced pain are peripheral tissue injury and inflammation, it is a prevalent type of persistent pain. Pain exists because of changes in the formation and immune cell recruitment and inflammatory substance release that cause nociceptors to become active [20]. Pain from maladaptive chronic inflammation typically lasts longer than the typical healing process, even though it is well recognized that pain from severe inflammation can protect against harmful stimuli and promote tissue repair [41].

Temporary muscle damage is usually triggered due to eccentric muscle contractions in skeletal muscles [43]. A prolonged increase in pain during exercise will lead to usually occurring 24 to 72 hours after exercise, DOMS (Delayed Onset Muscle Soreness) resolves in 4–6 days [46]. DOMS can also affect sports performance due to discomfort in the muscles and harm to the connective tissue including joint mechanics and changes in muscle function [8]. DOMS can also be considered an indirect indicator of muscle damage [37]. When a muscle is moved, DOMS symptoms most frequently manifest as discomfort and excruciating pain [15]. DOMS can also impair performance, which can lead to chronic injury and further debilitate chronic pain [30]. One of the impacts of DOMS is a decrease in maximal range of motion and strength. Micro-disruptions in the intracellular structure of muscle fibers are believed to be the source of this decrease [22]. Pain triggered by prolonged physical exercise will worsen if no effort is made to manage it.

In addition to the pain experienced, additionally, increased NF-κB (Nuclear Factor-kappa B) signaling from high-intensity exercise will result in inflammation [21]. Furthermore, when proinflammatory cytokines rise in reaction to pain, blood levels of TNF-a, or tumor necrosis factor-alpha, also increases [3]. Stress-induced and maladaptive events in skeletal muscle trigger an increase in the Nuclear Factor-kappa B (NF-κB) signaling cascade [38]. Additionally, the formation of T cell regulators involves specific roles of certain NF-κB complex types [7]. When skeletal muscle contracts, the mitochondria produce reactive oxygen species (ROS) as part of cellular respiration, which leads to proteolytic breakdown [34]. Apart from being triggered by oxidative stress brought on by exercise, NF-κB reacts to other types of cellular stress, such as elevations in proinflammatory cytokines [38]. Inflammatory reactions mediated by Nuclear Factor-kappa B (NF-κB) have been identified as a key mechanism that causes liver injury following vigorous exercise. Reactive oxygen species, DNA damage, exposure to pathogens, proinflammatory cytokines, and physical stress have all been shown to activate protein kinases, which in turn phosphorylate IkappaB kinase (IκB), causing NF-κB to translocate to the nucleus [13]. So, in short, the increased inflammation and pain suffered after strenuous physical exercise raises Nuclear Factor-kappa B (NF-κB) signaling levels.

As a possible remedy, an alternate approach is therefore required to solve the issue. One beneficial natural product that may have anti-inflammatory and antioxidant qualities is sea cucumber. A member of the phylum Echinodermata, sea cucumbers are invertebrates. This species is abundant in bioactive chemicals with several pharmacological and biological properties, including as anti-inflammatory, anti-cancer, antitumor, wound-healing, anticoagulant, antioxidant, antibacterial, and blood-sugar-regulating activities [35]. Sea cucumbers contain phenolics, proteins (peptides), carotenoids, lipids, and saponins, among other bioactive substances [18]. According to studies, sea cucumbers' phenolic compounds function as antioxidants that can delay the development of aging, prevent or lessen oxidative stress in cells, and help treat several diseases, including cancer and heart disease, and inflammation [36]. By giving free radicals hydrogen atoms or electrons to prevent free radical chain reactions, these phenolic compounds' antioxidant activity may help lessen oxidative damage caused by exposure to strong UV light and reactive oxygen species (ROS) [18].

The effects of post-exercise sea cucumber supplementation on NF-κB levels are still not fully understood. Understanding the underlying mechanisms related to the effects of post-exercise sea cucumber supplementation on NF-κB levels is essential to scientifically prove the effects of post-exercise sea cucumber supplementation. Therefore, the aim of this study was to analyze the effects of post-exercise sea cucumber supplementation on NF-κB levels as a biomarker of inflammation.

Material and methods. Study Design. The sample consisted of two groups: a control group and a treatment group. Using a random sample technique, participants were selected, and they were then divided into two groups: group K1 received a placebo, while group K2 received 500 mg of sea cucumber. The supplement form of sea cucumber is capsules.

Subjects. Eighteen men in good health took part in the study (Table 1 displays the subject characteristics). Inclusion and exclusion criteria were developed to determine if volunteers might meet the study's needs. College students with a normal Body Mass Index (BMI) who were between the ages of 20 and 25 met the inclusion criteria. Furthermore, regular exercise was not required of college students. Additionally, the study excluded people under the age of eighteen who had abnormal blood pressure prior to exercising. Lastly, if the subjects were taking nonsteroidal anti-inflammatory drugs (NSAIDs), they were excluded. The 18 study volunteers were divided into 2 groups, the physical exercise + sea cucumber treatment group (n= 9), and the control group with physical exercise + placebo (n= 9).

Research Instrument. Measurements of blood pressure, height, and weight, data collecting sheets, stationery, blood collection gear, sea cucumber supplements, and placebo capsules were among the materials utilized in this study.

Procedure. The data collection procedure in this study consisted of several steps. The subjects underwent a screening procedure before starting the study. Certain parameters that allowed information to be included or excluded in the analysis formed the basis of this approach. In addition, they gave informed consent, agreeing to take part in the study. Two groups were randomly selected from among the trial participants: the treatment group, which was given sea cucumber, and the placebo group. The treatment group was given sea cucumber supplementation at a dose of 500 mg, while the placebo group was given empty capsules. Sea cucumber supplementation was given in capsule form.

Three days were dedicated to data collection, beginning with the gathering of information on subject characteristics. Research subjects were prohibited from consuming anything before the implementation of the study. One day before the study, the research subjects were given directions to maintain a regular diet and rest pattern. They were then instructed to warm up. After that, exercise was done. The exercise performed is weight training with increasing intensity according to ability until fatigue. There are two tools used, the first is the Leg Machine which is used and given a maximum load. The second exercise is squad training using the Smith Machine which is also given a maximum load. All samples performed both types of exercise alternately. 24 hours after the weight training, the samples were directed to a room to have their blood drawn as pre-test data. After that, the samples were given supplements according to their respective groups. Subjects were given 500 mg sea cucumber intervention and placebo according to their respective groups. 48 hours after exercise, blood was taken for post-test data to measure NF-kB level. After the pretest and posttest blood samples were taken, laboratory analysis was carried out to examine NF-kB levels. This laboratory analysis was carried out at the Research Laboratory Installation of Airlangga University Hospital Surabaya. The method of examining NF-kB levels uses ELISA (Enzyme-linked immunosorbent assay). Finally, as a form of accountability, after reviewing the data, the researchers produced a written report.

CONSORT flowchart.

Statistical analysis. SPSS software was used to do statistical analysis after the data was collected. To determine the mean and standard error, a descriptive analysis was performed on the data. The Shapiro-Wilk test was also used in this investigation as a normality test. Using the paired t-test approach, a difference test was created to ascertain whether the data were normally distributed. The Wilcoxon signed-rank test was used to examine the data, however if the findings indicated otherwise.

Ethics. Prior to data collection, we obtained ethical approval from the Ethics Committee of

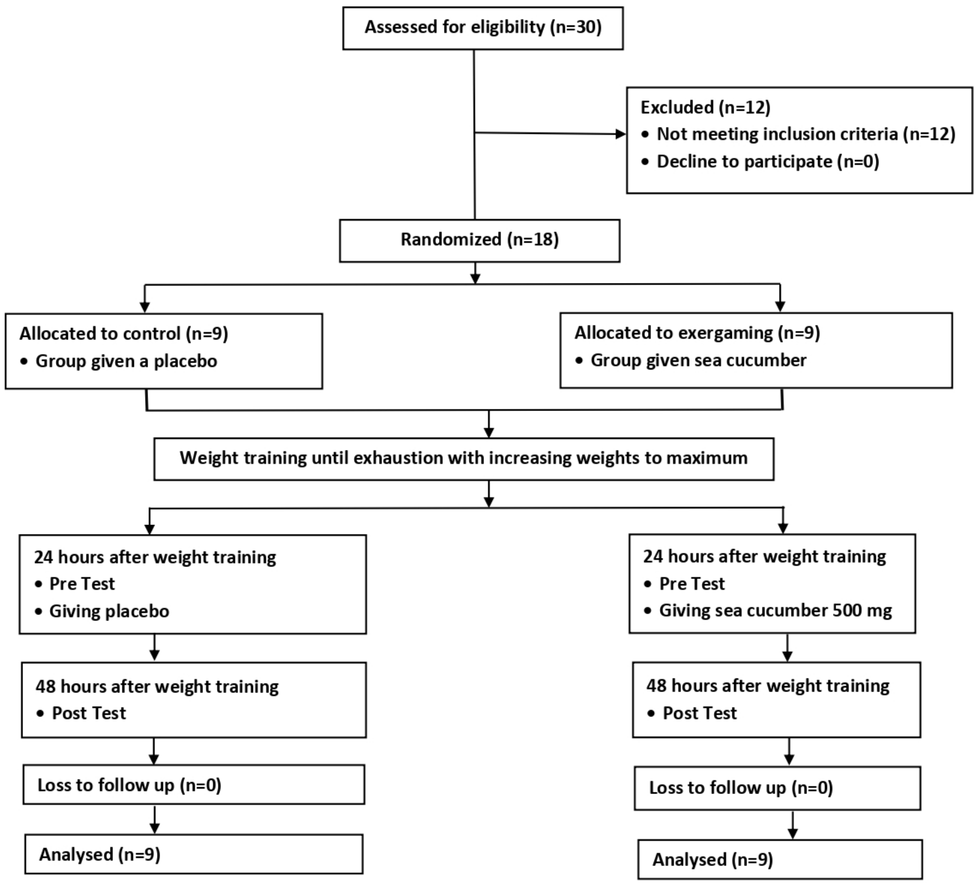

Fig. 1. The CONSORT flowchart

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Results. The statistics and details regarding the general attributes of the participants in Table 1 are presented in this section. We can gain a better understanding of each group's characteristics thanks to these statistics. The mean ± standard error is used to display the data. The t-test findings from the initial study indicated that there was no significant difference between K1 and K2 ($p \geq 0.05$).

Table 1

Characteristics of research subjects

Data	Group	N	x±SD	p-value
Age (y)	K1	9	22.33±0.79	0.873
	K2	9	22.55±0.91	
Height (cm)	K1	9	168.00±1.09	0.935
	K2	9	167.78±2.04	
Weight (kg)	K1	9	64.11±3.13	0.786
	K2	9	62.55±3.77	
BMI (kg/m2)	K1	9	22.67±0.98	0.815
	K2	9	22.24±1.31	
Systolic (mmHg)	K1	9	124.78±2.86	0.249
	K2	9	120.33±3.43	
Diastolic (mmHg)	K1	9	83.00±3.50	0.179
	K2	9	76.22±7.80	

Table 2

Normality test results

Data	Group	Shapiro-Wilk	
		n	p-value
NF-kB (pre-test)	K1	9	0.632
	K2	9	0.661
NF-kB (post-test)	K1	9	0.221
	K2	9	0.981

Based on the normality test in Table 2, the pre-test and post-test NF-kB data were normally distributed ($p>0.05$).

The results of NF-kB analysis between pre-test and post-test in each group are presented in Figure 2.

Information:

*There is a significant difference in the experimental group ($p<0.05$) and there is no significant difference in the control group ($p>0.05$).

Discussion. The purpose of this study was to determine how the effect of sea cucumber supplementation after exercise on NF-kB levels as a mediator of pro-inflammatory cytokines. It is

Table 3

Results of NF-kB (ng/L)

Difference Test Method	Group	P
Paired t-test	K1 (pre-test and post-test)	0.043*
	K2 (pre-test and post-test)	0.249

known from the analysis of the research that has been done in the control group that there is no significant decrease in NF-kB levels. The results of the study in the group given sea cucumber supplement intervention after exercise proved to reduce NF-kB levels as a mediator of inflammation. So, this confirms that the protective and anti-inflammatory effects contained in sea cucumbers are able to suppress NF-kB levels [12].

The inflammatory response occurs in someone who has done exercise especially eccentric movements with high intensity [27]. Increased mechanical strain and shards of bone extracellular matrix produced by high-intensity eccentric exercise are detected by the innate immune response receptors [29]. Cells that have been activated by physical exercise will trigger and stimulate NF-kB activation, thereby increasing inflammation [33]. According to previous theories, physical exercise increases NF-kB. NF-kB is known to play a role in the release of pro-inflammatory cytokines such as TNF-a and IL-6 [5]. In this instance, it is thought that an unchecked rise the prolonged muscle discomfort is caused by changes in pro-inflammatory cytokines, such as TNF-a, over a few days after high-intensity exercise.

From one to twenty-four hours following exercise, an immunologic reaction also takes place, demonstrating that neutrophils enter the muscle and collect where damage has occurred [28; 32]. Following physical activity, muscle injury is also characterized by anomalies in the muscles' ultrastructure that cause macrophages to produce more pro-inflammatory cytokines [29]. When muscle injury occurs, pro-inflammatory cytokines and neutrophils cooperate to regulate the pro-inflammatory response [16]. To control the reaction to inflammation, macrophages release anti-inflammatory cytokines in response to increasing pro-inflammatory cytokines [31]. Since muscle discomfort is caused by the control

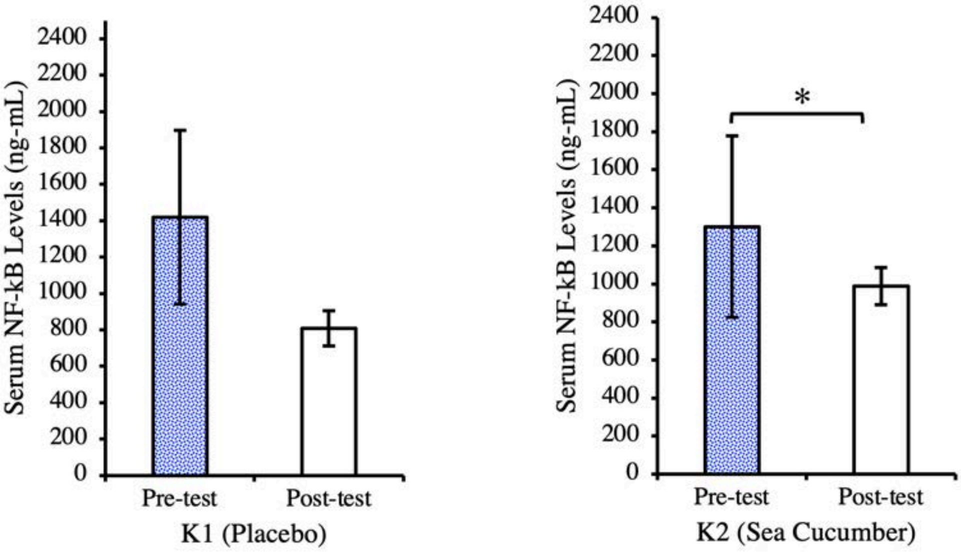

Fig. 2. Group K1, which was given placebo after exercise, could not significantly reduce NF-kB levels (p>0.05). Group K2, which was given sea cucumber supplements after exercise, could significantly reduce NF-kB levels (*p<0.05). Data are presented as mean ± standard error

of NF-kB expression, we think that sea cucumber supplements that suppress NF-kB are crucial to therapeutic efforts.

When performing maximal physical exercise, ROS increases [28]. The IκB kinase complex, which phosphorylates NF-kB inhibitory proteins, is directly altered and activated by ROS [17]. NF-kB dimers are released from their inhibitory complex as a result of this process, allowing them to begin gene transcription by entering the nucleus [14]. On the other hand, ROS levels can negatively impact NF-kB regulation during maximal physical exercise when they rise above physiological limits, which frequently happens in reaction to environmental stressors, cytokines, or infections [23]. Because excessive ROS disrupts the unfavorable comments systems that typically regulate the pathway, it can result in prolonged activation of NF-kB. Critical cysteine residues in NF-kB cascade proteins, including IKK, can be directly changed by ROS, resulting in the long-term activation of [39]. Moreover, ROS-induced DNA damage may indirectly promote NF-kB activation. DNA damage sensors like ATM and ATR kinases phosphorylate NF-kB essential modulator (NEMO), a component of the IKK complex, in response to DNA strand breaks and other lesions. These phosphorylation events can connect genotoxic stress to inflammatory responses by increasing IKK and NF-kB activation [6].

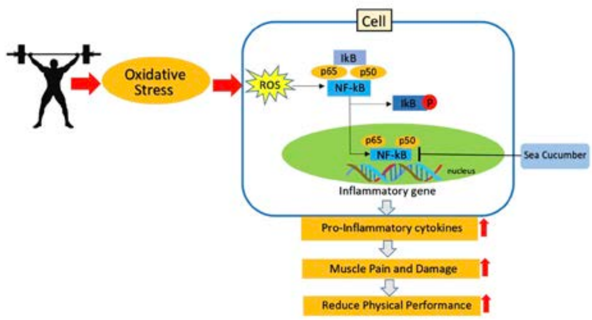

Fig. 3. The mechanism of sea cucumber in inhibiting NF-kB after maximal physical exercise

The nutritional value of sea cucumbers is very high with characteristics of high protein and low fat, making it a type of seafood that has the potential to be consumed [26]. Antioxidants present in sea cucumbers also possess the capacity to purify free radicals so as to prevent oxidation. Sea cucumbers' high phenolic content is linked to anti-inflammatory antioxidants [18]. Phenolic is an antioxidant content of sea cucumber that acts as a scavenger of several oxidizing species, such as peroxy radicals, hydroxyl radicals, and superoxide anion, and is a single scavenger of oxygen free radicals [2]. Cinnamic acid, ferulic acid, gallic acid, and P-cumaric acid, catechins, rutin, pyrogallol and quercetin are phenolic chemicals that are frequently present in sea cucumbers. According to research findings, phenolic compounds can promote reduce oxidation, impede the MAPK signaling pathway to have anti-inflammatory effects and prevent the production of pro-inflammatory cytokines such nitric oxide synthase (iNOS), nitric acid (NO), TNF-α, IL-1β, and PGE2 [19]. According to one study, the peptides in sea cucumbers function as reducing agents that can shield cells from oxidative stress by triggering signaling responses in cells, including nuclear factor NF-kB signaling, phosphoinositide 3-kinase (PI3K) or Akt signaling pathways, and mitogen-activated protein kinase (MAPK) [24].

Supplementing high-fat rats with sea cucumbers has also been demonstrated in other research to lower TNF-alpha levels [11]. Supplementing with sea cucumber has also been shown to lower NF-kB levels, according to other study findings [45]. Prior laboratory research that found sea cucumber extract may have anti-inflammatory and antioxidant properties supports this study as well [9]. The significant amounts of polyphenols found in sea cucumbers lend credence to this finding. Polyphenolic substances can lessen the harmful effects of proinflammatory signals and offer protection against reactive oxygen species in cells [9]. Furthermore, another study discovered that sea cucumber extract’s phenolic content exhibited potent antioxidant activity [1].

By stabilizing free radicals, these extracts act as sources of hydrogen to stop the oxidation process. Bioactive compounds like phenolic acids (gallic acid, caffeic acid, pyrrolic acid, and vanillic acid) help fight off free radicals [1]. As a result, the antioxidant activity is supported by these polyphenolic compounds. The results of this study are supported by research suggesting that sea cucumber extract could have anticancer properties due to sea cucumber bioactive compounds such antioxidants and anti-inflammatory agents [42]. These strong substances have the ability to combat nitric oxide and free radicals, as well as maybe block certain proteins that cause oxidative stress [42]. By preventing the KEAP1 and iNOS proteins from interacting with the DLG NRF2 motif, sea cucumber extract helps to prevent oxidative stress in cells [4]. Therefore, it is evident how important it is to take sea cucumber supplements as an extra nutrient to lower inflammation levels after physical activity.

Conclusions. Sea cucumber supplementation at a dose of 500 mg after exercise was shown to significantly reduce NF-kB levels. The strong antioxidant content in sea cucumber has the potential to reduce muscle damage and inflammation after exercise. So that this will affect the reduction of pain. For future research recommendations, the effect of sea cucumber supplementation on other inflammatory biomarkers such as IL-6 can be investigated. This is very important to explore the molecular mechanisms that occur. So that the relationship between signal transduction pathways that are interrelated with each other can be known. Limitations of this study are the small sample size and short intervention time. We also recommend further research on chronic physical exercise combined with sea cucumber supplementation to evaluate its effect on other biomarkers associated with inflammatory processes after exercise.

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Conflict of Interest. The authors declare no conflict of interest.

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References

1. Aatab, F., Bellali, F., Aboudamia, F.Z., Errhif, A., & Kharroubi, M. (2023). Phenolic compounds and in vitro antioxidant activity of spray-dried and freeze-dried aqueous extracts of sea cucumber (Holothuria tubulosa). *Journal of Applied Biology and Biotechnology*, *11*(6), 158–167. https://doi.org/10.7324/JABB.2023.130990.

2. Ajiboye, B.O., Shonibare, M.T., & Oyinloye, B.E. (2020). Antidiabetic activity of watermelon (Citrullus lanatus) juice in alloxan-

induced diabetic rats. *Journal of Diabetes and Metabolic Disorders*, *19*(1), 343–352. https://doi.org/10.1007/s40200-020-00515-2.

3. Ayubi, N., Kusnanik, N.W., Herawati, L., Komaini, A., Mutohir, T.C., Gemaini, A., Nugroho, A.S., & Pranoto, N.W. (2023). Effects of Curcumin on Inflammatory Response During Exercise-Induced Muscle Damage (Literature Review). *Biointerface Research in Applied Chemistry*, *13*(2), 1–19.

4. Ayubi, N., Padmasari, D.F., Komaini, A., Syafawi, A., Ardha, M.A.Al, Dafun, P.B., Ming, J.W., Lesmana, H.S., & Putri, D.R.S. (2024). Phytochemical Compounds in Sea Cucumber Have the Potential to Reduce Oxidative Stress and Inflammation Due to Exercise: Systematic Review. *Physical Education Theory and Methodology*, *24*(1), 158–168. https://doi.org/10.17309/tmfv.2024.1.19.

5. Ayubi, N., Kusnanik, N.W., Herawati, L., Callixte, C., Ming, J.W., Aljunaid, M., Mario, D.T., Komaini, A., & Padmasari, D.F. (2024). Potential of Curcumin to Reduce Serum Nuclear Factor-Kappa B (NF-kB) Levels After High-Intensity Exercise. *Retos*, *57*, 616–622. https://doi.org/10.47197/retos.v57.103902.

6. Bensimon, A., Aebersold, R., & Shiloh, Y. (2011). Beyond ATM: The protein kinase landscape of the DNA damage response. *FEBS Letters*, *585*(11), 1625–1639. https://doi.org/10.1016/j.febslet.2011.05.013.

7. Blanchett, S., Boal-Carvalho, I., Layzell, S., & Seddon, B. (2021). NF-kB and Extrinsic Cell Death Pathways – Entwined Do-or-Die Decisions for T cells. *Trends in Immunology*, *42*(1), 76–88. https://doi.org/10.1016/j.it.2020.10.013.

8. Boguszewski, D., Krawczyk, A., Dębek, M., & Adamczyk, J.G. (2024). The effects of foam rolling applied to delayed-onset muscle soreness of the quadriceps femoris after Tabata training. *Biomedical Human Kinetics*, *16*(1), 203–209. https://doi.org/10.2478/bhk-2024-0021.

9. Carletti, A., Cardoso, C., Lobo-Arteaga, J., Sales, S., Juliao, D., Ferreira, I., Chainho, P., Dionísio, M.A., Gaudêncio, M.J., Afonso, C., Lourenço, H., Cancela, M.L., Bandarra, N.M., & Gavaia, P.J. (2022). Antioxidant and Anti-inflammatory Extracts from Sea Cucumbers and Tunicates Induce a Pro-osteogenic Effect in Zebrafish Larvae. *Frontiers in Nutrition*, *9*(May), 1–13. https://doi.org/10.3389/fnut.2022.888360.

10. Cohen, S.P., Vase, L., & Hooten, W.M. (2021). Chronic pain: an update on burden, best practices, and new advances. *The Lancet*, *397*(10289), 2082–2097. https://doi.org/10.1016/S0140-6736(21)00393-7.

11. Dewi, L., Agung, A., Agung, I., & Nataswari, S. (2025). *Anti-inflammatory and antioxidant effects of sea cucumber extract in mitigating hepatic TNF– α elevation induced by high-fat diet*. 1–5.

12. Fagbohun, O.F., Thilakarathna, W.P.D.W., Zhou, J., Lehmann, C., Jiao, G., & Rupasinghe, H.P.V. (2024). Sea Cucumber and Blueberry Extracts Suppress Inflammation and Reduce Acute Lung Injury through the Regulation of NF-kB/MAPK/JNK Signaling Pathway in Lipopolysaccharide-Treated C57BL/6 Mice. *Molecules*, *29*(7). https://doi.org/10.3390/molecules29071511.

13. Gao, C., Liu, Y., Jiang, C., Liu, L., Li, J., Li, D., Guo, X., Wang, Z., Yang, Y., Liu, L., Yao, P., & Tang, Y. (2020). Intensive running enhances NF-kB activity in the mice liver and the intervention effects of quercetin. *Nutrients*, *12*(9), 1–12. https://doi.org/10.3390/nu12092770.

14. Gloire, G., Legrand-Poels, S., & Piette, J. (2006). NF-kB activation by reactive oxygen species: Fifteen years later. *Biochemical Pharmacology*, *72*(11), 1493–1505. https://doi.org/10.1016/j.bcp.2006.04.011.

15. Han, K., Kwon, O., Jung, S.Y., Park, I.H., Hwang, M.S., Park, S.Y., Hwang, E.H., & Lee, J.H. (2020). Jakyakgamcho-tang in the relief of delayed-onset muscle soreness in healthy adults: Study protocol for a randomized, double-blind, placebo-controlled, crossover design clinical trial. *Trials*, *21*(1), 1–10. https://doi.org/10.1186/s13063-020-4119-4.

16. Hody, S., Croisier, J.-L., Bury, T., Rogister, B., & Leprince, P. (2019). Eccentric Muscle Contractions: Risks and Benefits. *Frontiers in Physiology*, *10*, 536. https://doi.org/10.3389/fphys.2019.00536.

17. Hong, Y., Boiti, A., Vallone, D., & Foulkes, N.S. (2024). Reactive Oxygen Species Signaling and Oxidative Stress: Transcriptional Regulation and Evolution. *Antioxidants*, *13*(3). https://doi.org/10.3390/antiox13030312.

18. Hossain, A., Dave, D., & Shahidi, F. (2022). Antioxidant Potential of Sea Cucumbers and Their Beneficial Effects on Human Health. *Marine Drugs*, *20*(8), 1–22. https://doi.org/10.3390/md20080521.

19. Hossain, A., Dave, D., & Shahidi, F. (2020). Northern sea cucumber (Cucumaria frondosa): A potential candidate for functional food, nutraceutical, and pharmaceutical sector. *Marine Drugs*, *18*(5). https://doi.org/10.3390/md18050274.

20. Hwang, S.M., Chung, G., Kim, Y.H., & Park, C.K. (2019). El papel de las maresinas en el dolor inflamatorio: Función de macrófagos en la regeneración de heridas. *Diario Internacional de Ciencias Moleculares, 20*(23).

21. Jung, S., Ahn, N., Park, J., & Kim, K. (2018). Effects of 8 Weeks Calorie Reduction and Resistance Exercise on Traf2-NFkB-mTOR and SIRT1-FoxO1 Signal Expression of Cardiac Muscle in High-fat Induced Obese Middle-Aged Rats. *Exercise Science*. https://doi.org/10.15857/ksep.2018.27.2.126.

22. Kaczmarek, A., Kaczmarek, M., Ciałowicz, M., Clemente, F.M., Wolański, P., Badicu, G., & Murawska-Ciałowicz, E. (2021). The role of satellite cells in skeletal muscle regeneration – the effect of exercise and age. *Biology, 10*(10), 1–18. https://doi.org/10.3390/biology10101056.

23. Lingappan, K. (2018). NF-kB in oxidative stress. *Current Opinion in Toxicology, 7*, 81–86. https://doi.org/10.1016/j.cotox.2017.11.002.

24. Lu, M., Mishra, A., Boschetti, C., Lin, J., Liu, Y., Huang, H., Kaminski, C.F., Huang, Z., Tunnacliffe, A., & Kaminski Schierle, G.S. (2021). Sea Cucumber-Derived Peptides Alleviate Oxidative Stress in Neuroblastoma Cells and Improve Survival in C. elegans Exposed to Neurotoxic Paraquat. *Oxidative Medicine and Cellular Longevity*. https://doi.org/10.1155/2021/8842926.

25. Malange, K.F., Navia-Pelaez, J.M., Dias, E.V., Lemes, J.B.P., Choi, S.H., Dos Santos, G.G., Yaksh, T.L., & Corr, M. (2022). Macrophages and glial cells: Innate immune drivers of inflammatory arthritic pain perception from peripheral joints to the central nervous system. *Frontiers in Pain Research,* 3(October), 1–20. https://doi.org/10.3389/fpain.2022.1018800.

26. Mao, J., Li, S., Fu, R.R., Wang, Y., Meng, J., Jin, Y., Wu, T., & Zhang, M. (2023). Sea Cucumber Hydrolysate Alleviates Immunosuppression and Gut Microbiota Imbalance Induced by Cyclophosphamide in Balb/c Mice through the NF-κB Pathway. *Foods, 12*(8). https://doi.org/10.3390/foods12081604.

27. Markus, I., Constantini, K., Hoffman, J.R., Bartolomei, S., & Gepner, Y. (2021). Exercise-induced muscle damage: mechanism, assessment and nutritional factors to accelerate recovery. In *European Journal of Applied Physiology*. https://doi.org/10.1007/s00421-020-04566-4.

28. Meng, Q. (2024). *The Impact of Physical Exercise on Oxidative and Nitrosative Stress: Balancing the Benefits and Risks*. 1–26.

29. Nanavati, K., Rutherfurd-Markwick, K., Lee, S.J., Bishop, N.C., & Ali, A. (2022). Effect of curcumin supplementation on exercise-induced muscle damage: a narrative review. *European Journal of Nutrition*. https://doi.org/10.1007/s00394-022-02943-7.

30. Nobari, H., Aquino, R., Clemente, F.M., Khalafi, M., Adsuar, J.C., & Pérez-Gómez, J. (2020). Description of acute and chronic load, training monotony and strain over a season and its relationships with well-being status: A study in elite under-16 soccer players. *Physiology and Behavior*, *225*. https://doi.org/10.1016/j.physbeh.2020.113117.

31. Nonnenmacher, Y., & Hiller, K. (2018). Biochemistry of proinflammatory macrophage activation. *Cellular and Molecular Life Sciences: CMLS*, *75*(12), 2093–2109. https://doi.org/10.1007/s00018-018-2784-1.

32. Paulsen, Gø., Crameri, R., Benestad, H.B., Fjeld, J.G., Mørkrid, L., Hallén, J., & Raastad, T. (2010). Time course of leukocyte accumulation in human muscle after eccentric exercise. *Medicine and Science in Sports and Exercise*, *42*(1), 75–85. https://doi.org/10.1249/MSS.0b013e3181ac7adb.

33. Pavis, G.F., Jameson, T.S.O., Dirks, M.L., Lee, B.P., Abdelrahman, D.R., Murton, A.J., Porter, C., Alamdari, N., Mikus, C.R., Wall, B.T., & Stephens, F.B. (2021). Improved recovery from skeletal muscle damage is largely unexplained by myofibrillar protein synthesis or inflammatory and regenerative gene expression pathways. *American Journal of Physiology – Endocrinology and Metabolism*, *320*(2), E291–E305. https://doi.org/10.1152/AJPENDO.00454.2020.

34. Powers, S.K., Radak, Z., Ji, L.L., & Jackson, M. (2024). Reactive oxygen species promote endurance exercise-induced adaptations in skeletal muscles. *Journal of Sport and Health Science*, *13*(6), 780–792. https://doi.org/10.1016/j.jshs.2024.05.001.

35. Rasyid, A., Putra, M.Y., & Yasman. (2023). Antibacterial and antioxidant activity of sea cucumber extracts collected from Lampung waters, Indonesia. *Kuwait Journal of Science, 50*(4), 615–621. https://doi.org/10.1016/j.kjs.2023.03.012.

36. Senadheera, T.R.L., Hossain, A., Dave, D., & Shahidi, F. (2023). Antioxidant and ACE-Inhibitory Activity of Protein Hydrolysates

Produced from Atlantic Sea Cucumber (Cucumaria frondosa). *Molecules*, *28*(13). https://doi.org/10.3390/molecules28135263.

37. Stewart, I.B., Moghadam, P., Borg, D.N., Kung, T., Sikka, P., & Minett, G.M. (2020). Thermal infrared imaging can differentiate skin temperature changes associated with intense single leg exercise, but not with delayed onset of muscle soreness. *Journal of Sports Science and Medicine*, *19*(3), 469–477.

38. Townsend, J.R., Stout, J.R., Jajtner, A.R., Church, D.D., Beyer, K.S., Oliveira, L.P., La Monica, M.B., Riffe, J.J., Muddle, T.W.D., Baker, K.M., Fukuda, D.H., Roberts, M.D., & Hoffman, J.R. (2016). Resistance exercise increases intramuscular NF-kB signaling in untrained males. *European Journal of Applied Physiology*, *116*(11–12), 2103–2111. https://doi.org/10.1007/s00421-016-3463-2.

39. Turillazzi, E., Neri, M., Cerretani, D., Cantatore, S., Frati, P., Moltoni, L., Busardò, F.P., Pomara, C., Riezzo, I., & Fineschi, V. (2016). Lipid peroxidation and apoptotic response in rat brain areas induced by long-term administration of nandrolone: The mutual crosstalk between ROS and NF-kB. *Journal of Cellular and Molecular Medicine*, *20*(4), 601–612. https://doi.org/10.1111/jcmm.12748.

40. Varrassi, G., Alon, E., Bagnasco, M., Lanata, L., Mayoral-Rojals, V., Paladini, A., Pergolizzi, J.V., Perrot, S., Scarpignato, C., & Tölle, T. (2019). Towards an Effective and Safe Treatment of Inflammatory Pain: A Delphi-Guided Expert Consensus. *Advances in Therapy*, *36*(10), 2618–2637. https://doi.org/10.1007/s12325-019-01053-x.

41. Vergne-Salle, P., & Bertin, P. (2021). Chronic pain and neuroinflammation. *Joint Bone Spine*, *88*(6), 105222. https://doi.org/10.1016/j.jbspin.2021.105222.

42. Wargasetia, T.L., Ratnawati, H., Widodo, N., & Widyananda, M.H. (2023). Antioxidant and Anti-inflammatory Activity of Sea Cucumber (Holothuria scabra) Active Compounds against KEAP1 and iNOS Protein. *Bioinformatics and Biology Insights*, *17*. https://doi.org/10.1177/11779322221149613.

43. Wiecha, S., Posadzki, P., Prill, R., & Płaszewski, M. (2024). Physical Therapies for Delayed Onset Muscle Soreness: A Protocol for an Umbrella and Mapping Systematic Review with Meta-Meta-Analysis. *Journal of Clinical Medicine*, *13*(7), 1–11. https://doi.org/10.3390/jcm13072006.

44. Zhang, X., Zhu, L., Wang, X., Xia, L., & Zhang, Y. (2023). Advances in the role and mechanism of miRNA in inflammatory pain. *Biomedicine and Pharmacotherapy*, *161*, 114463. https://doi.org/10.1016/j.biopha.2023.114463.

45. Zhao, Q., Xue, Y., Wang, J.-feng, Li, H., Long, T.-teng, Li, Z., Wang, Y.– ming, Dong, P., & Xue, C.-hu. (2012). In vitro and in vivo anti-tumour activities of echinoside A and ds-echinoside A from Pearsonothuria graeffei. *Journal of the Science of Food and Agriculture*, *92*(4), 965–974. https://doi.org/10.1002/jsfa.4678.

46. Zulaini, Harahap, N.S., Siregar, N.S., & Zulfahri. (2021). Effect Stretching and Recovery on Delayed Onset Muscle Soreness (DOMS) after Exercise. *Journal of Physics: Conference Series*. https://doi.org/10.1088/1742-6596/1811/1/012113.

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