Specialty Journal of Pharmacognosy, Phytochemistry, and Biotechnology
ISSN: 3062-441X
2022, Volume 2, Page No: 73-80

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

The Impact of Moderate Intensity Exercise and Lemon Peel Essential Oil on Immune Function During the COVID-19 Pandemic

Novita Sari Harahap[1]*, Diky Setya Diningrat[2], Nurhamida Sari Siregar[1]

[1]Department of Sports Sciences, Faculty of Sports Sciences, University of Negeri Medan, Medan, Indonesia.
[2]Department of Biology, Faculty of Mathematics and Natural Sciences, University of Negeri Medan, Indonesia.

***E-mail** ✉ novitahrp@unimed.ac.id

Received: 17 September 2022; **Revised:** 27 November 2022; **Accepted:** 29 November 2022

ABSTRACT

Regular moderate-intensity exercise can increase the effectiveness of the body's endogenous antioxidants, and potentially boost immune defenses against viral infections. The bioflavonoids in lemon peel essential oil, known for their antioxidant properties, also help protect against free radical damage while acting as immunomodulators. This study aimed to evaluate the potential benefits of consistent moderate exercise and lemon peel essential oil on the immune response during the COVID-19 pandemic. The study involved randomly dividing 20 white rats into two groups, each consisting of 10 animals. Group P1 participated in 40-minute moderate-intensity swimming sessions, while group P2 underwent the same swimming routine and also received 0.05 milliliters of lemon peel essential oil per hour before the swimming sessions. The results showed that in the RDF group, the total antioxidant capacity (TAC) increased from 320.34 ± 44.05 µmol (pre-test) to 353.01 ± 70.22 µmol (post-test), and the C-reactive protein (CRP) level decreased from 0.54 ± 0.11 ng/ml (pre-test) to 0.49 ± 0.04 ng/ml (post-test). Similarly, the RE group experienced an increase in TAC from 338.15 ± 29.14 µmol (pre-test) to 356.48 ± 44.34 µmol (post-test) and a decrease in CRP levels from 0.56 ± 0.04 ng/ml (pre-test) to 0.53 ± 0.09 ng/ml (post-test). However, no statistically significant differences were observed in TAC ($P > 0.05$) or CRP ($P > 0.05$) levels after the exercise, and no significant differences were observed between the two groups ($P > 0.05$).

Keywords: Regular exercise, Antioxidant, Immunomodulator, Lemon peel essential

How to Cite This Article: Harahap NS, Diningrat DS, Siregar NS. The Impact of Moderate Intensity Exercise and Lemon Peel Essential Oil on Immune Function During the COVID-19 Pandemic. Spec J Pharmacogn Phytochem Biotechnol. 2022;2:73-80. https://doi.org/10.51847/fCcjs2PJIN

Introduction

In early 2020, a new type of pneumonia caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) rapidly spread worldwide and was named COVID-19 [1-3]. The World Health Organization categorized this outbreak as both a pandemic and a global health emergency. The repercussions of this epidemic have been vast, influencing economic systems, social behaviors, and individual lifestyles, particularly regarding respiratory health. Discussions on the disease's diagnosis, management, and preventive measures remain ongoing [4, 5]. The infection disrupts the body's immune response, contributing to tissue damage [6].

COVID-19 is caused by an RNA virus measuring between 120 and 160 nm in size. This virus is part of a family that includes six human-infecting coronaviruses: 229E, NL63, OC43, HKU1, SARS-CoV, and MERS-CoV [7]. The virus responsible for COVID-19 belongs to the betacoronavirus genus. Phylogenetic analysis shows that SARS-CoV-2 is closely related to the SARS virus from the 2002-2004 outbreak [8]. Consequently, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses [9].

The pandemic has prompted an increased focus on physical fitness and exercise. Alongside regular physical activity, maintaining a healthy lifestyle and proper nutrition is crucial for boosting immunity and preventing COVID-19 infection [10]. It is advisable to exercise indoors during quarantine to avoid exposure to the virus. Activities such as walking, swimming, stair climbing, sit-ups, and yoga are all effective forms of exercise that can

be incorporated into daily routines [11]. Initial studies suggest that enhancing the activity of endogenous antioxidants such as catalase can help improve resistance to viral infections. Therefore, regular physical exercise can be considered a form of immunotherapy, providing an affordable and significant way to enhance the quality of life [12].

Indonesia, known for its tropical climate, is home to a wide variety of plants that offer numerous benefits to humans, animals, and the environment. Lemons, which are commonly consumed in Indonesia for their vitamin C content, are just one example. According to Indonesian Essential Oil: The Scents of Natural Life (2011), there are approximately 40 plant species in the country that are suitable for essential oil production.

Essential oils are volatile compounds extracted from different parts of plants, including stems, leaves, flowers, seeds, bark, fruits, roots, and rhizomes. These oils contain various bioactive compounds, such as terpenes, acetone, phenols, aldehydes, alcohols, esters, and acids, which are present in many plant species [13]. Lemon peel essential oil, which contains powerful antioxidants, plays a crucial role in protecting the body from oxidative stress. Moreover, these bioactive compounds can help regulate immune function. Immunomodulation refers to the process of altering immune system activity, which can either suppress or stimulate immune responses [14].

During physical activity, oxygen consumption can increase by 10 to 15 times compared to resting conditions. In cases of maximal exertion, the oxygen supply to body tissues may rise to 20 times, while oxygen uptake within muscle fibers can reach up to 100 times higher than at rest. This substantial increase in oxygen utilization may lead to the formation of free radicals due to the leakage of electrons from the mitochondrial respiratory chain. Consequently, exercise is closely associated with increased oxygen consumption and elevated oxidative stress levels [15].

Several studies have demonstrated that free radicals generated during muscle contraction, particularly under conditions of tissue hypoxia, play a physiological role in promoting exercise adaptation. These reactive oxygen species (ROS) function as signaling molecules that stimulate gene expression, enhancing the endogenous production of antioxidants and contributing to the body's defense against oxidative stress [16]. However, excessive production of free radicals may disrupt the balance between pro-oxidants and antioxidants, leading to oxidative stress. This condition often results in lipid peroxidation, cellular damage, and reperfusion injury, which impairs oxygen and nutrient delivery, triggers ischemia, and causes microvascular damage. Furthermore, oxidative stress can activate inflammatory pathways, stimulating the release of C-reactive protein (CRP), a well-established biomarker of inflammation and infection. Typically, oxidative stress biomarkers, including CRP, are measured in plasma, providing a stable medium for their assessment [17].

CRP is an acute-phase protein synthesized by the liver in response to inflammatory stimuli, particularly those mediated by pro-inflammatory cytokines. Elevated CRP levels in the serum reflect the body's inflammatory response and may indicate muscle injury resulting from exercise-induced stress [18]. Regular moderate-intensity exercise has been shown to enhance the total antioxidant capacity (TAC) by promoting the synthesis of enzymatic antioxidants such as catalase, as well as increasing levels of non-enzymatic antioxidants, including uric acid, albumin, ceruloplasmin, and metallothionein. Moreover, regular exercise can reduce lipid peroxidation and mitigate oxidative damage. TAC is commonly used to assess the antioxidant status of biological samples and serves as an indicator of the body's ability to neutralize free radicals [19].

The improvement of endogenous antioxidant defenses is influenced by several factors, including the type, duration, and intensity of exercise, as well as the individual's training status and nutritional intake. Trained individuals exhibit less DNA damage from strenuous exercise compared to untrained individuals. In addition to regular physical activity, consuming antioxidant-rich fruits is crucial for strengthening the immune system, especially during the COVID-19 pandemic. Antioxidants are compounds that, even at low concentrations, can inhibit oxidative processes by neutralizing free radicals. They achieve this by donating an electron to unstable molecules without becoming free radicals themselves, thus preserving cellular integrity [20].

Antioxidants are classified into two main groups: endogenous (enzymatic) antioxidants, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and exogenous (non-enzymatic) antioxidants, obtained from diet or supplements, including glutathione, vitamin C, vitamin E, carotenoids, uric acid, and zinc [21]. Several studies have reported that the consumption of antioxidant-rich foods, such as fruits and vegetables, can lower CRP levels. Bioactive compounds like anthocyanins are believed to significantly contribute to CRP reduction, although other antioxidants may also exert similar effects. When free radicals are produced within physiological limits, endogenous antioxidant systems can adequately neutralize them. However, in cases where endogenous antioxidants are insufficient, the intake of exogenous antioxidants becomes necessary [22].

This study aimed to assess the potential benefits of consistent moderate exercise and lemon peel essential oil on immune response during the COVID-19 pandemic. Citrus peel essential oil was selected as an intervention in this study because, in addition to its content of bioactive metabolites, it offers potential antioxidant properties that may modulate oxidative stress and inflammatory responses.

Materials and Methods

This study utilized an experimental method with a post-test control group design. The research subjects comprised male Wistar strain white rats (*Rattus norvegicus*), weighing between 180 to 200 grams and aged approximately 3 to 4 months. A total of 20 rats were used in this experiment. The animals were randomly assigned into two groups, each consisting of ten rats. Group P1 was subjected to moderate-intensity swimming exercise for 40 minutes. In contrast, group P2 underwent the same swimming protocol but received an additional treatment of 0.05 milliliters of lemon peel essential oil administered orally every hour for one hour before the swimming activity.

Total antioxidant capability (TAC) test

Measurement of TAC levels was performed using the QuantiChromTM Antioxidant Assay Kit (DTAC-100) supplied by Bioassay Systems. This method is based on the principle that, under correct assay conditions, the generated Cu+ ions interact with a dye reagent to form a colored complex. The resulting color intensity corresponds directly to the TAC concentration in the sample and is quantified by measuring absorbance at a wavelength of 570 nm. To prepare the standard, 5 µL of the provided standard solution was mixed with 245 µL of distilled water to achieve a final concentration of 1 mM Trolox. Subsequently, 20 µL of either the standard solution or the test sample was added to each well of a 96-well flat-bottom clear microplate. For the working reagent, 100 µL of reagent A was combined with 8 µL of reagent B for each well. Then, 100 µL of this working solution was added to each well containing the standard or sample. The microplate was gently mixed and left to incubate at room temperature for 10 minutes. Following incubation, the absorbance was measured at 570 nm using a plate reader.

C-reactive protein (CRP) test

Quantification of CRP levels was carried out using the Human CRP ELISA Kit (Catalog No: E1798Hu, Bioassay Technology Laboratory), employing the standard ELISA procedure. The wells of the microplate were pre-coated with human CRP antibodies. Samples were added to the wells, allowing CRP present in the samples to bind to the immobilized antibodies. Subsequently, a biotin-conjugated anti-human CRP antibody was introduced, forming a complex with the bound CRP. This was followed by the addition of Streptavidin-HRP, which binds to the biotinylated antibody. After an incubation period, the wells were washed to eliminate any unbound Streptavidin-HRP. A substrate solution was then added, triggering a colorimetric reaction proportional to the CRP concentration in the sample. The reaction was terminated by the addition of a stop solution, and absorbance was measured at a wavelength of 450 nm.

Statistical analyses

Data analysis was performed using SPSS software version 20.0. The data were expressed as mean values accompanied by standard deviations. Statistical comparisons between the two experimental groups were conducted using the Student's t-test, with a significance threshold set at $P < 0.05$.

Results and Discussion

Based on the results of the statistical analysis, it was observed that total antioxidant capability (TAC) levels increased in both experimental groups following the intervention. In group P1, which only performed moderate-intensity swimming, TAC levels rose by 5.14%. Meanwhile, group P2, which received lemon peel essential oil supplementation before swimming, demonstrated a higher increase in TAC levels, reaching 9.25%. Despite this difference in the percentage increase, statistical analysis indicated that the variation in TAC levels between the two groups was not significant ($P = 0.896$; $P > 0.05$), as presented in **Table 1**.

Additionally, the C-reactive protein (CRP) levels in both groups showed a decrease after the treatment period. The reduction in CRP levels was more pronounced in group P2, which experienced a 10.22% decrease, whereas

group P1 recorded a lower reduction of 5.66%. Nevertheless, the comparative analysis revealed no statistically significant difference in CRP level reduction between the two groups (P = 0.296; P > 0.05), as detailed in **Table 1**.

Table 1. TAC and CRP levels in the group that engaged in regular exercise and the group that engaged in regular exercise with antioxidants

Variable (n = 10)		P1 group	P2 group	*P*
		Mean ± SD	Mean ± SD	
TAC (µmol)	Pre-test	338.15 ± 29.14	320.34 ± 44.05	0.896
	Post-test	356.48 ± 44.34	353.01 ± 70.22	
	% increased	5.14%	9.25%	
CRP (ng/ml)	Pre-test	0.56 ± 0.04	0.54 ± 0.11	0.296
	Post-test	0.53 ± 0.09	0.49 ± 0.04	
	% decreased	5.66%	10.22%	

Note: P1 group: regular exercise; P2 group: regular exercise+antioxidant

In individuals experiencing mild to moderate COVID-19 symptoms, the immune response is characterized by an elevation in CD8 T lymphocytes, an increase in antibody-secreting cells (ASCs), and a higher count of follicular helper T cells circulating in the bloodstream, accompanied by a progressive rise in SARS-CoV-2 specific IgM and IgG antibodies. Interestingly, in patients with non-severe forms of COVID-19, no noticeable elevation in chemokines or pro-inflammatory cytokines was detected [23].

Engaging in consistent physical activity enables the body to adapt and develop mechanisms to cope with physiological stressors, transforming them into beneficial stimuli. While intense physical exertion can trigger elevated levels of C-reactive protein (CRP), habitual exercise, on the other hand, has been shown to contribute to lowering CRP concentrations [24].

The immune system, comprising both the innate (non-specific) and adaptive (specific) components, is essential for preserving the body's homeostasis and defense mechanisms. The suppression of immune function observed during the resting phase in individuals subjected to repeated exercise without antioxidant supplementation may result from the cumulative stress hormone response, particularly elevated cortisol levels, coupled with increased anti-inflammatory cytokine production, including CRP [25].

Furthermore, during strenuous exercise, leukocyte activity is altered due to elevated plasma concentrations of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), alongside anti-inflammatory cytokines. Muscle contraction primarily drives the elevation of plasma IL-6 levels observed during exercise; however, prolonged physical activity can eventually suppress IL-6 production from monocytes. Exercise serves as an immunomodulatory factor, regulating immune responses and protecting against cellular damage caused by various diseases. In response to exercise-induced physiological stress, the hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland. This leads to the release of adrenocorticotropic hormone (ACTH), which in turn influences the adrenal cortex to produce cortisol — a key hormone that plays a vital role in regulating immune responses, particularly under conditions of oxidative stress [26].

It has been demonstrated that a combination of regular physical exercise and the intake of lemon peel essential oil can lead to improvements in total antioxidant capacity (TAC), increased catalase activity, and reduced CRP levels in trained individuals compared to exercise alone. However, the observed differences in the increase of TAC, catalase activity, and reduction in CRP levels between the groups are not statistically significant. The enhancement in TAC levels noted in both study groups is likely attributable to regular exercise promoting the endogenous antioxidant defense system, aiding in the neutralization of free radicals, and contributing to overall physical fitness. Optimal physical condition enhances the body's capacity to produce its antioxidant defenses. Continuous physical activity facilitates tissue adaptation to oxidative stress, thus preventing free radical-induced damage to muscles [27].

Repeated exercise fosters tissue adaptation against free radical damage, thereby safeguarding the body from oxidative stress and protecting muscle tissue from injury [28]. Free radicals, characterized by unpaired electrons, exhibit high reactivity as they seek to stabilize themselves by capturing electrons from surrounding molecules.

This reaction may lead to the generation of new radicals, perpetuating a chain reaction that can eventually result in damage to cellular structures such as mitochondria, cells, and tissues [29].

Regular physical activity has been shown to reduce the production of harmful free radicals while stimulating the biosynthesis of antioxidant enzymes. Through consistent exercise, TAC levels improve, and oxidative stress is mitigated. Furthermore, regular physical activity enhances DNA repair mechanisms by upregulating the expression of genome repair enzymes within skeletal muscle tissue. While acute bouts of aerobic exercise can transiently increase oxidative stress, long-term aerobic exercise promotes the production of endogenous antioxidants, thereby lessening oxidative stress-related damage. This improvement in the body's antioxidant defense system is supported by research demonstrating increases in erythrocyte glutathione peroxidase (GPx) activity and catalase levels following regular exercise [30]. The enhancement of antioxidant enzyme activity is a well-recognized adaptation resulting from consistent exercise engagement [31].

The enhancement of antioxidant defense mechanisms during physical activity arises from both the mobilization of naturally occurring (endogenous) antioxidants and the release of tissue-stored antioxidants into circulation. However, when exercise is performed under overtraining conditions, the body's ability to adapt to oxidative challenges becomes impaired, leading to elevated oxidative stress levels, alongside reductions in total antioxidant capacity (TAC) and catalase enzyme activity. Evidence has shown that marathon running induces a decline in TAC and an increase in DNA damage within human lymphocytes, indicating oxidative stress [32]. Similarly, athletes engaged in acute endurance exercise also demonstrate reduced TAC and heightened lipid peroxidation, further confirming the oxidative imbalance resulting from intense physical activity [33].

The reduction in antioxidant capacity following strenuous exercise reflects a disruption in the balance between oxidants and antioxidants, favoring oxidative stress due to the excessive generation of free radicals. Interestingly, participants who underwent regular training while receiving lemon peel essential oil supplementation experienced a greater elevation in TAC levels. This enhancement is attributed to the secondary metabolites of the polyphenol class within lemon peel essential oil, which act as potent antioxidants capable of neutralizing free radical species. The antioxidant defense mechanism functions by delaying, preventing, or eliminating oxidative damage through various pathways, including scavenging free radicals, chelating metal ions, inhibiting enzymes that generate free radicals, and activating endogenous antioxidant systems [34].

Lemon peel essential oil is particularly rich in polyphenols, which surpass other antioxidants in abundance and possess significant reducing activity. These compounds also exhibit non-toxic immunomodulatory properties, enabling them to effectively scavenge free radicals without causing harm to biological systems [35].

This study's results are in line with prior research demonstrating the antioxidant capacity of red dragon fruit. The flavonoid compounds found in red dragon fruit can neutralize free radicals produced during physical exercise, thereby preventing oxidative stress-related damage [36]. Moreover, a reduction in C-reactive protein (CRP) levels was observed across both groups involved in the study. This decline is attributed to the anti-inflammatory benefits of regular physical exercise, which operates through several mechanisms, such as downregulation of inflammatory signaling pathways and stimulation of myokines in muscle tissue that promote the production of anti-inflammatory cytokines like IL-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10) [37].

Regular physical activity can lead to a decrease in CRP levels at rest by inhibiting cytokine production and exerting potential antioxidant effects. Consequently, exercise-induced reductions in pro-inflammatory biomarkers, including CRP, have been documented [38]. Notably, participants in the regular training group who received red dragon fruit supplementation exhibited a more pronounced reduction in CRP levels. This effect is linked to the antioxidant constituents of red dragon fruit, which aid in lowering CRP concentrations. In addition to flavonoids, red dragon fruit contains other bioactive compounds such as anthocyanins, β-carotene, tocopherol, phenolics, and ascorbic acid. Anthocyanins, in particular, have demonstrated the ability to inhibit the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), both of which are regulated by nuclear factor-kappa B (NF-kB) — a key transcription factor responsible for activating various inflammatory genes, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [39].

Furthermore, in this investigation, the group subjected to regular exercise and supplemented with Citrus Peel Essential Oil experienced significant reductions in CRP levels. This anti-inflammatory effect is attributed to the bioactive components of lemon peel essential oil, particularly flavonoids, which suppress the production of pro-inflammatory cytokines such as TNF-α, IL-6, and interferon-gamma (IFN-γ) [28].

Conclusion

In summary, regular physical activity enhances the body's production of internal antioxidants, which helps to mitigate oxidative stress and protect cellular integrity. The generation of reactive oxygen species (ROS) at moderate levels during exercise activates specific transcription factors that stimulate the expression of antioxidant genes. When exercise is performed consistently, the body's ability to defend against free radicals becomes robust. Additionally, minyak atsiri kulit lemon, which contains flavonoids, boosts total antioxidant capacity (TAC), acting as an external antioxidant to further enhance the body's overall antioxidant capacity.

Acknowledgments: The author would like to thank all individuals who played a role in the success of this study. This research was supported financially by the DIPA Fund of Medan State University, under Decree No. 0001/UN33.8/PL-PNBP/2021 issued by the Rector of UNIMED.

Conflict of Interest: None

Financial Support: This work was financially supported by the DIPA Medan State University.

Ethics Statement: This study adhered to the ethical guidelines set forth by the Declaration of Helsinki (World Medical Association, 2002) and received approval from the Animal Research Ethics Committees (AREC) of the University of North Sumatra (approval number: No.0425/KEPH-FMIPA/2021).

References

1. Alghamdi A, Ibrahim A, Alraey M, Alkazemi A, Alghamdi I, Alwarafi G. Side effects following COVID-19 vaccination: a cross-sectional survey with age-related outcomes in Saudi Arabia. J Adv Pharm Educ Res. 2021;11(3):119-25.
2. Alghamdi A, Ibrahim A, Almutairi R, Joseph M, Alghamdi G, Alhamza A. A cross-sectional survey of side effects after COVID-19 vaccination in Saudi Arabia: Male versus female outcomes. J Adv Pharm Educ Res. 2021;11(2):51-6.
3. Siyal FJ, Shaikh ZA, Ahmed SZ, Shahid MA, Agha F, Khoso M, et al. Anxiety among COVID-19 physicians during the pandemic in the health care center of the rural region. Arch Pharm Pract. 2020;11(4):91-3.
4. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl). 2020;133(9):1015-24.
5. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433.
6. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424-32.
7. Riedel S, Morse S, Mietzner T, Miller S. Jawetz, Melnick, & Adelberg's Medical Microbiology. 28th ed. New York: McGraw-Hill Education/Medical; 2019. p. 617-22.
8. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
9. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020. doi:10.1038/s41564-020-0695-z
10. Campbell JP, Turner JE. Debunking the myth of exercise-induced immune suppression: redefining the impact of exercise on immunological health across the lifespan. Front Immunol. 2018;9:648.
11. Alkhatib A. Antiviral functional foods and exercise lifestyle prevention of coronavirus. Nutrients. 2020;12(9):2633. doi:10.3390/nu12092633
12. Samadi M, Shirvani H, Rahmati-Ahmadabad S. A study of possible role of exercise and some antioxidant supplements against coronavirus disease 2019 (COVID-19): a cytokines related perspective. Apunt Sport Med. 2020;55(207):115-7.
13. Ali B, Al-Wabel NA, Shams S, Ahamad A, Khan SA, Anwar F. Essential oils used in aromatherapy: a systemic review. Asian Pac J Trop Biomed. 2015;5(8):601-11.
14. Singh N, Tailang M, Mehta SC. A review on herbal plants as immunomodulators. Int J Pharm Sci Res. 2016;7(9):3602-10.

15. Accattato F, Greco M, Pullano SA, Carè I, Fiorillo AS, Pujia A, et al. Effects of acute physical exercise on oxidative stress and inflammatory status in young, sedentary obese subjects. PloS one. 2017;12(6):e0178900. doi:10.1371/Journal.Pone.0178900
16. Pastor R, Tur JA. Antioxidant supplementation and adaptive response to training: a systematic review. Curr Pharm Des. 2019;25(16):1889-912. doi:10.2174/1381612825666190701164923
17. Gyurászová M, Kovalčíková A, Janšáková K, Šebeková K, Celec P, Tóthová Ľ. Markers of oxidative stress and antioxidant status in the plasma, urine and saliva of healthy mice. Physiol Res. 2018;67(6):921-34. doi:10.33549/physiolres.933866
18. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8(3):201-17. doi:10.1016/j.jshs.2018.09.009
19. Rubio CP, Hernández-Ruiz J, Martinez-Subiela S, Tvarijonaviciute A, Ceron JJ. Spectrophotometric assays for total antioxidant capacity (TAC) in dog serum: an update. BMC Vet Res. 2016;12(1):166.
20. Baghaiee B, Aliparasti MR, Almasi S, Siahkuhian M, Baradaran B. Antioxidant expression response to free radicals in active men and women fallowing to a session incremental exercise; numerical relationship between antioxidants and free radicals. Asian J Sports Med. 2016;7(2):e29901.
21. Rao PS, Kalva S, Yerramilli A, Mamidi S. Free radicals and tissue damage: role of antioxidants. Free Radic Antioxid. 2011;1(4):2-7. doi:10.5530/ax.2011.4.2
22. Navarro P, de Dios O, Jois A, Gavela-Pérez T, Gorgojo L, Martín-Moreno JM, et al. Vegetable and fruit intakes are associated with hs-CRP levels in pre-pubertal girls. Nutrients. 2017;9(3):224.
23. Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med. 2020;26(4):453-5.
24. Jürimäe J, Tillmann V, Purge P, Jürimäe T. Acute inflammatory response to prolonged sculling in competitive male rowers. J Sports Med Phys Fitness. 2016;56(11):1368-75.
25. Guyton AC, Hall JE. Textbook of Medical Physiology. 13th ed. Philadelphia (PA): Elsevier Saunders; 2016.
26. Nurul SR, Asmah R. Variability in nutritional composition and phytochemical properties of red pitaya (Hylocereus polyrhizus) from Malaysia and Australia. Int Food Res J. 2014;21(4):1689-97.
27. Franzoni F, Federighi G, Fusi J, Agosta V, Cerri E, Banducci R, et al. Physical exercise improves total antioxidant capacity and gene expression in rat hippocampal tissue. Arch Ital Biol. 2017;155(1-2):1-10.
28. Suen J, Thomas J, Kranz A, Vun S, Miller M. Effect of flavonoids on oxidative stress and inflammation in adults at risk of cardiovascular disease: a systematic review. Healthcare (Basel). 2016;4(3):69.
29. He F, Li J, Liu Z, Chuang CC, Yang W, Zuo L. Redox mechanism of reactive oxygen species in exercise. Front Physiol. 2016;7:486.
30. Farhat F, Dupas J, Amérand A, Goanvec C, Feray A, Simon B, et al. Effect of exercise training on oxidative stress and mitochondrial function in rat heart and gastrocnemius muscle. Redox Rep. 2015;20(2):60-8.
31. Kruk J, Aboul-Enein HY, Kładna A, Bowser JE. Oxidative stress in biological systems and its relation with pathophysiological functions: the effect of physical activity on cellular redox homeostasis. Free Radic Res. 2019;53(5):497-521.
32. Cheng AJ, Jude B, Lanner JT. Intramuscular mechanisms of overtraining. Redox Biol. 2020;35:101480.
33. Yang MY, Hung TW, Wang CJ, Tseng TH. Inhibitory effect of nelumbo nucifera leaf extract on 2-acetylaminofluorene-induced hepatocarcinogenesis through enhancing antioxidative potential and alleviating inflammation in rats. Antioxidants (Basel). 2019;8(9):329.
34. Zhao C, Wang F, Lian Y, Xiao H, Zheng J. Biosynthesis of citrus flavonoids and their health effects. Crit Rev Food Sci Nutr. 2020;60(4):566-83.
35. Musumeci L, Maugeri A, Cirmi S, Lombardo GE, Russo C, Gangemi S, et al. Citrus fruits and their flavonoids in inflammatory bowel disease: an overview. Nat Prod Res. 2020;34(1):122-36.
36. Harahap NS, Lelo A, Purba A, Sibuea A, Amelia R, Zulaini Z. The effect of red-fleshed pitaya (Hylocereus polyrhizus) on heat shock protein 70 and cortisol expression in strenuous exercise induced rats. F1000Res. 2019;8:130.
37. Chirco KR, Potempa LA. C-reactive protein as a mediator of complement activation and inflammatory signaling in age-related macular degeneration. Front Immunol. 2018;9:539.
38. Phillips CM, Dillon CB, Perry IJ. Does replacing sedentary behaviour with light or moderate to vigorous physical activity modulate inflammatory status in adults? Int J Behav Nutr Phys Act. 2017;14(1):138.

39. Ferrer MD, Capó X, Martorell M, Busquets-Cortés C, Bouzas C, Carreres S, et al. Regular practice of moderate physical activity by older adults ameliorates their anti-inflammatory status. Nutrients. 2018;10(11):1780.