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REGULAR EXERCISE OF MODERATE INTENSITY AND LEMON PEEL ESSENTIAL OIL AS IMMUNOMODULATOR DURING COVID-19

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ABSTRACT

Regular exercise can increase the sensitivity of endogenous antioxidants so that it can increase the immune system against viral infections. Antioxidants like bioflavonoids, which are found in lemon peel essential oil, help shield the body from the damaging effects of free radicals and immunomodulators. The goal of this research was to find out whether or not frequent moderate-intensity exercise and the lemon peel essential oil can boost immunity during the Covid-19 Pandemic. The experimental animals were separated into two groups at random, with ten white rats in each group: group P1 consisted of rats that participated in swimming activities of moderate intensity for forty minutes; group P2 consisted of rats that participated in swimming activities of moderate intensity for forty minutes, but also received 0.05 milliliters of lemon peel essential oil every hour for the preceding hour before the rats participated in swimming activities. The average TAC level in the RDF group (pre-test 320.34 ± 44.05 μmol; post-test 353.01 ± 70.22 μmol) and average CRP level (pre-test 0.54 ± 0.11 ng/ml; post-test 0.49 ± 0.04 ng/ml). The average TAC level in the RE groups (pre-test 338.15 ± 29.14 μmol; post-test 356.48 ± 44.34 μmol) and average CRP level (pre-test 0.56 ± 0.04 ng/ml; post-test 0.53 ± 0.09 ng/ml). There were no significantly increased TAC ($p>0.05$) and decreased CRP ($p>0.05$) after the exercise test compared to before. There were no substantial differences between the two groups ($p>0.05$).

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Introduction

Early in the year 2020, a new strain of pneumonia caused by Severe Acute Respiratory Syndrome Coronavirus-2 swept the globe and was quickly dubbed "coronavirus disease 2019" (COVID-19) (SARS-CoV-2) [1-3]. The World Health Organization has labeled this outbreak a pandemic and a public health emergency of international concern. The effects of this epidemic on the economy, social interactions, and individual lifestyles have been far-reaching, especially with regard to respiratory problems in humans. There is still a great deal of debate over this illness, particularly in regard to the diagnosis, treatment, and prevention of the condition [4, 5]. Infection with the Coronavirus is linked to dysregulation of the body's immune system, which contributes to tissue damage [6].

Coronavirus is an RNA virus with a particle size of 120-160 nm that consists of six human-infecting coronaviruses: alphacoronavirus 229E, alphacoronavirus NL63, betacoronavirus OC43, betacoronavirus HKU1, Severe Acute Respiratory Illness Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [7]. The coronavirus that causes COVID-19 is a member of the genus betacoronavirus. The findings of phylogenetic research indicate that this virus belongs to the same subgenus as Sarbecovirus, the coronavirus that was responsible for the outbreak of Severe Acute Respiratory Illness (SARS) in 2002-2004 [8]. The International Committee on Taxonomy of Viruses proposed the name SARS-CoV-2 based on this information [9].

During this pandemic, more people are paying attention to athletics and other forms of physical activity than ever before. In addition to engaging in regular physical activity, engaging in good lifestyle habits and eating nutritious food are highly important for keeping fit and maintaining body immunity to prevent the transmission of COVID-19 [10]. During quarantine, it is best to exercise indoors to avoid breathing in any coronavirus particles. Everyday activities like walking, swimming, stair

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climbing,it-ups, and yoga are all examples of how sports movements can be incorporated into one's life [11]. Preliminary research indicated that a heightened sensitivity of endogenous antioxidants like catalase could improve resistance to coronavirus infection. In this way, regular exercise training can be viewed as a form of immunotherapy and may constitute a highly cost-effective intervention that can significantly enhance people's quality of life. In this way, regular exercise training can be viewed as a form of immunotherapy, and may constitute a highly cost-effective intervention that can significantly enhance people's quality of life [12].

Indonesia is a tropical country with a lot of different plants and animals that need to be protected and grown. One of them is the variety of plants, which helps people, animals, and the environment in many ways. Lemons have been used as a fruit juice drink in Indonesia for a long time due to the country's need for a high intake of vitamin C. Indonesian Essential Oil: The Scents of Natural Life (2011) reports that the country's abundant flora includes about 40 plant species that could provide raw materials for essential oil manufacturers.

Essential oils are a type of volatile secondary metabolite found in oil-shaped plants (volatile). This essential oil is extracted from the entire plant, including the stems, leaves, flowers, seeds, bark, fruits, roots, and rhizomes. Essential oils contain terpenes, acetone, phenols, aldehydes, alcohols, esters, and acids, and these compounds are found in nearly all plant species [13]. Essential oil from lemon peel contains bioactive components that function as antioxidants, defending the body from damage caused by free radicals. Furthermore, the immune system's function can be modulated by these bioactive substances. Immunomodulatory refers to the ability to alter the immune system, and its two main types are immunosuppressants and immunostimulants [14].

At the time of physical practice session, there can be an increase in oxygen consumption 10 to 15 times compared to at rest; even during heavy physical activity to the maximum, the supply of oxygen throughout the body increases 20 times, while the intake of oxygen in muscle fibers can reach 100 times that of rest. This excessive use of oxygen may trigger the formation of free radicals through the disconnection of electrons from the respiratory chain. Exercise is associated with higher oxygen consumption and oxidative stress [15].

Some research has found that free radicals formed by tissue hypoxia during muscle contractions have a physiological role in fitness adaptation. The adaptive process can occur because free radicals act as signaling molecules to stimulate gene expression, increasing the endogenous production of antioxidants, and thereby preventing oxidative stress in the body [16]. The formation of free radicals can cause imbalances with the endogenous antioxidant activity known as oxidative stress, so lipid peroxidation occurs. Oxidative stress also occurs due to reperfusion injury, which decreases the amount of oxygen and nutrients, resulting in ischemic processes and microvascular damage. Oxidative stress may trigger inflammatory stimuli which then stimulate the release of the C-reactive protein as a marker of infection. Oxidative stress markers are usually measured in plasma, a stable environment for biomarkers [17].

C-reactive protein (CRP) is a protein produced by the liver, and its levels in serum can increase in inflammatory response as biochemical markers of the inflammatory response and muscle injury stimulated by the production of proinflammatory cytokines [18]. Regular Exercise at moderate intensity performed regularly can increase Total Antioxidant Capacity (TAC) by modulating enzymatic antioxidant syntheses like Catalase and non-enzymatic antioxidants (uric acid, albumin, ceruloplasmin, metallothionein) and can reduce lipid peroxidation. Total antioxidant capacity (TAC) is a commonly used analyte for assessing the antioxidant status of biological samples and may determine the antioxidant response to free radicals [19].

The increase in endogenous antioxidants depends on the type and duration of exercise, trained or untrained, and nutrient intake. In trained individuals, DNA damage as a result of strenuous exercise is less than in untrained individuals. In addition to regular exercise, it also regularly takes fruits rich in antioxidants to boost its immune system, particularly during the COVID-19 pandemic. Antioxidants are compounds at low levels capable of inhibiting the oxidation of target molecules so that they can fight or neutralize free radicals [20]. Antioxidants work by donating one electron to an oxidizing compound so that the activity of the oxidant compound can be inhibited. What is unique about antioxidant work is that antioxidants do not become free radicals after releasing electrons as if other cells were giving electrons. Such antioxidants work such as neutralizing the reactive properties of free radical molecules. This works with antioxidants such as the neutralization of the reactive properties of free radical molecules.

Antioxidants consist of two groups: endogenous antioxidants (enzymatic antioxidants) and exogenous antioxidants (non-enzymatic antioxidants). The endogenous antioxidants are superoxide dismutase (SOD), catalase and glutathione peroxide (GPx). Exogenous antioxidants from dietary supplements or foods are glutathione, vitamin C, vitamin E, carotenoids, uric acid, and zinc [21].

Some studies suggest that the consumption of high antioxidants such as vegetables, fruits, and other sources of antioxidants will reduce C-reactive protein levels. Metabolites such as anthocyanins have the potential to participate in a substantial influence on C-reactive protein decrease, although other types of antioxidant content can also lower C-reactive protein levels. When free radicals are not in excess, the human body can neutralize them using endogenous antioxidant defense systems. If endogenous antioxidants are not sufficient, then the body needs external antioxidants [22]. The intervention of citrus peel essential oil was chosen because, in addition to containing metabolites, compounds that have the potential as antioxidants are also widely cultivated by the People of Indonesia.

Based on the facts that have been disclosed, it is necessary to conduct a study to evaluate the Total Antioxidant Capacity and markers inflammatory like C-reactive protein following regular exercise and citrus peel essential oil.

Materials and Methods

The approach to conducting research is experimental, and it makes use of a post-test group design. The subjects of the study were white rats (Rattus norvegicus) of the Wistar strain, which ranged in body weight from 180-200 grams and had an average age of 3-4 months. There were as many as 20 male heads in the group. The experimental animals were separated into two groups at random, with ten white rats in each group: group P1 consisted of rats that participated in swimming activities of moderate intensity for forty minutes; group P2 consisted of rats that participated in swimming activities of moderate intensity for forty minutes, but also received 0.05 milliliters of lemon peel essential oil every hour for the preceding hour before the rats participated in swimming activities.

Total Antioxidant Capability (TAC) Test

TAC level determination using QuantiChromTM Antioxidant Assay Kit (DTAC-100) by Bioassay Systems. The TAC test principle states that the resulting Cu+ will form a colorful complex with a dye reagent if the test is performed correctly. The sample has a TAC concentration that is proportional to the color intensity measured at 570 nm. Blend 5 μL from standard with 245 μL dH2O (final 1 mM Trolox). Fill the wells on a 96-well flat-bottom clear plate with 20 L standards. Fill each well of the 96-well plate with 20 L of each sample. Mix 100 L of reagent A and 8 L of reagent B for each dosing well to make enough working reagents for the sample and standard wells. Pour 100 L of working reagent into each assay well. Incubate at room temperature for 10 minutes after mixing the plate. OD570NM should be read from a plate drive.

C-reactive Protein (CRP) Test

The amount of CRP determination using Human CRP Elisa Kit, catalog no: E1798Hu (Bioassay Technology Laboratory), with ELISA method. The plate has been primed with human CRP antibodies, subsequently introduced to the sample, and binds to the coated antibodies on the wells. Subsequently, a biotinylated antibody of human C-reactive protein is added and binds to the C-reactive protein in the sample. Streptavidin-HRP is next added, which binds to the Biotinylated C-reactive protein antibody. Unbound streptavidin-HRP is removed from the sample during the washing step that follows the incubation step. The substrate solution is then added after that, and the color intensifies in a manner that is directly proportional to the amount of human CRP that is present. Following the addition of the acid-arresting solution, the reaction is finished, and its absorbance at 450 nm is measured.

Statistical Analyses

Data was collected by analytical statistical testing using SPSS software version 20.0. The results were shown using mean and standard deviation format. To compare the two groups, Student t-test analyses were used ($p<0.05$).

Results and Discussion

The results of the statistical analysis showed that both groups' TAC levels went up after training. The TAC went up by 5.14 percent in the P1 group and by 9.25 percent in the P2 group. However, no significant difference can be seen between the P1 group and the P2 group in terms of average TAC rate ($p= 0.896$; $P>0.05$) (**Table 1**). The findings also revealed that after therapy, average CRP levels in both groups were reduced, which in the P2 group decreased by 10.22% compared to the P1 group, which decreased by 5.66%. However, there is not a significant difference between the RE groups and the RDF groups in terms of the average CRP rate reduction ($p= 0.296$; $P>0.05$) (**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	
	% decreased	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 patients with mild to moderate COVID-19 symptoms, the immune response is caused by an increase in CD8 T cells, an increase in antibody-secreting cells (ASCs), and an increase in follicular helper T cells in the blood, as well as a gradual rise in SARS-CoV-2 IgM/IgG. In patients with non-severe COVID-19 symptoms, there was no increase in chemokines and pro-inflammatory cytokines [23]. The body will be able to respond to regular exercises that are carried out constantly to acquire a coping mechanism that converts stressors into helpful stimulators if these activities are carried out regularly. C-reactive protein levels can be triggered by heavy physical exercise, but conversely if regular exercise can have an impact on reduced C-reactive

protein levels [24].

The immune system, composed of non-specific (natural/innate/native) and specific (adaptive/acquired) immune systems, maintains the body's integrity. The cumulative effect of repeated exercise with the result of increased stress hormones, especially cortisol, and anti-inflammatory cytokine C-reactive protein may account for the depressed immunity observed in the resting state of the exercise group that did not receive antioxidants [25].

The function of leukocytes, including inflammatory cytokines (such as TNF- and IL-1), as well as anti-inflammatory cytokines, will be affected when plasma concentrations are raised to high levels by rigorous physical exercise. Muscle contraction is the source of the observed rise in the plasma levels of cytokines generated by IL-6. However, sustained activity over several hours will inhibit IL-6 production by monocytes. Exercising your body has been shown to have immunomodulatory effects, meaning it can influence the immune system and prevent disease-related cell damage. In response to exercise-induced stress, the hypothalamus can release corticotrophin-realizing hormone (CRH), which in turn signals the anterior pituitary. Adrenocorticotrophin hormone (ACTH) is released by the pituitary and can stimulate or otherwise affect the adrenal cortex, where cortisol is produced. When the body is under oxidative stress, cortisol levels rise as a signal that has a major impact on the immunological response [26].

Regular exercise and regular consumption of lemon peel essential oil can increase TAC levels, and catalase, and decrease CRP levels among trained individuals, as opposed to regular exercise only. The increase in TAC levels, catalase, and the decrease in CRP levels is not a significant difference. The increase in TAC levels happens in both groups because regular physical exercise can increase the production of endogenous antioxidants causing free radicals in elimination and good fitness. The right physical condition will improve the body's ability to produce endogenous antioxidants. Regular exercise induces tissue adaptability to free radicals, thereby preventing oxidative stress in the body and preventing muscular damage [27].

Regular exercise results in the adaption of tissues to free radicals, thereby preventing oxidative stress in the body and preventing muscular damage [28]. The absence of a pair of electrons causes the compound to be very responsive in searching for partners by attacking and binding to the electrons of surrounding molecules. This compound, if it encounters a new radical, will form new radicals again and so on, which ultimately the number continues to grow, so there will be a chain reaction and may damage mitochondria, cells, and tissues [29].

Regular exercise reduces free radicals that damage the body and promotes the biosynthesis of antioxidant enzymes. Regular physical exercise can improve TAC and reduce oxidative stress. Regular exercise can also reduce DNA damage by increasing the expression of genome repair enzymes in skeletal muscles. Acute aerobic exercise can increase oxidative stress production, while regular aerobic exercise can increase the production of endogenous antioxidants and reduce the effects of oxidative stress. Regular exercise improves antioxidant defenses, based on studies conducted that glutathione peroxidase (GPx) of erythrocytes and catalase increases after regular exercise [30]. An increase in antioxidant enzymes can occur in exercise if carried out regularly as it causes adaptations against oxidative stress. In the body of athletes who do regular exercise, as a result of the adaptation of the athlete's antioxidant defense system, there is a reduction in the creation of free radicals, which is a positive outcome [31].

Increased defenses of these antioxidants are due to the transmission of endogenous antioxidants and antioxidants that accumulate in tissue into circulation along with exercise. Exercise with overtraining conditions inhibits tissues and organs' adaptation to exercise, causing increased oxidative stress and also decreased Total Antioxidant Capacity and catalase. There was a decrease in TAC as well as an increase in DNA oxidation from human lymphocytes after marathon running [32]. A decrease in Total Antioxidant Capacity and an increase in lipid peroxidation also occur in athletes following acute endurance training [33].

This decrease in antioxidant capacity indicates that oxidative stress occurs due to an imbalance between free radicals and antioxidants due to increased oxidants. There was a higher increase in TAC levels in the regular training group given lemon peel essential oil secondary metabolites of the polyphenol group that can act as antioxidants by capturing free radical compounds. Antioxidants' mechanism of action to reduce free radical compounds is to delay, prevent, and eliminate oxidative damage from target molecules by cooling free radicals, and metal events, lowering enzyme levels that help form free radicals, and stimulating internal antioxidant enzymes [34].

Lemon peel essential oil contains polyphenols that are relatively more abundant than other types of antioxidants, have a potential reduction activity and are non-toxic immunomodulators for the task of scavenging free radicals [35].

The findings of this study are consistent with earlier research indicating that red dragon fruit possesses antioxidant capacity. The red dragon fruit metabolite compound containing flavonoids can neutralize free radicals formed by physical exercise to prevent oxidative stress [36]. Decreased CRP levels occurred in both groups due to regular and regular physical exercise having an overall anti-inflammatory influence mediated by several pathways, including increased control of inflammatory signaling pathways, stimulating myokine muscles for il-1ra and IL-10 production [37].

Regular physical exercise can reduce CRP levels at rest through a mechanism of decreased cytokine production and possible antioxidant effects. As a result of the exercise, pro-inflammatory biomarkers like the C-reactive protein were reduced [38]. In the regular training group given red dragon fruit, there was a decrease in higher levels of C-reactive protein because red dragon fruit contains antioxidants that can lower C-reactive protein levels. Antioxidants in red dragon fruits and flavonoids also contain anthocyanins, β-carotene, tocopherol, phenolics, and ascorbic acid. Anthocyanins present in red dragon fruit inhibit cyclooxygenase-2 (COX-2) or inhibit the inducible nitric oxide (iNOS) protein of a gene involved in many inflammatory processes. These genes are transcribed by nuclear factor-kB (NF-kB). NF-kB also plays a role in transcribing some pro-

inflammatory cytokines such as TNF-α, IL-1β, and Il-6 [39].

In this study, the Citrus Peel Essential Oil made the CRP levels go down in the group that did regular exercise. This happened because the lemon peel essential oil made the body's inflammatory response go down. The anti-inflammatory properties of flavonoids stem from their ability to prevent the production of inflammatory cytokines such as tumour necrosis factor-alpha (TNF-), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) [28].

Conclusion

In conclusion, the increased production of endogenous antioxidants during regular exercise can prevent oxidative stress that can damage cells and their components. Reactive Oxygen Species (ROS) in mild-moderate levels formed during physical exercise activate transcription factors that play a role in expressing endogenous antioxidant genes in the body. Antioxidant defense mechanisms against free radicals will be adequate if physical exercise is carried out continuously. Minyak atsiri kulit lemon can increase TAC levels and lemon peel essential oil contains Flavonoids that work as external antioxidants and have a positive impact on increasing the overall antioxidant capacity of the body.

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Conflict of interest: None

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Ethics statement: Ethical Approval. This research procedure is in accordance with the principles of the Declaration of Helsinki (World Medical Association, 2002) and has been approved by the Animal Research Ethics Committees (AREC) University of North Sumatra (approval number: No.0425/KEPH-FMIPA/2021).

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