Trad. Med. J., September-December 2021
Vol. 26(3), p 197-203
ISSN-p : 1410-5918 ISSN-e : 2406-9086

Submitted : 19-08-2021
Revised : 16-09-2021
Accepted : 18-10-2021

Supplementation of *Garcinia mangostana* Linn and *Vasconcellea pubescens* A.DC Extract Reduced Exercise-induced Oxidative Stress in Rats

Heru Sasongko[1*], Sugiyarto[2], Renita Wahyu Nur Hidayati[1], Bayu Anggoro Saputro[1]
[1] Department of Pharmacy, Universitas Sebelas Maret
[2] Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Sebelas Maret

ABSTRACT

The objective of this study was to see how supplementation with Garcinia mangostana extract (GME) and Vasconcellea pubescens extract (VPE) affected exercise performance and oxidative stress in intensely exercised rats. Twenty-five male rats were used in the study. Rats were divided into five groups: normal, stress oxidative control, combination GME:VPE (50:50), combination GME:VPE (75:25), and combination GME:VPE (25:75) groups. The antioxidant activity of a single extract from the literature was used to make the percentage comparison between extracts. The chronic exercise was done by swimming at 10 m/day for two weeks. Rats in the acute exercise groups were treated by swimming on the pail containing water. Blood samples were collected from the orbital sinus to determine hematological parameters. Liver tissue samples for the analysis of malondialdehyde (MDA) and glutathione (GPx) markers. Data analysis was performed statistically using One Way ANOVA. The combination of GME and VPE was shown to be effective in reducing oxidative stress and increasing MDA and GPx enzyme activity. The administration of both extracts also showed changes in the hematological profile.
Key words: exercise; hematology; malondialdehyde; total flavonoid.

INTRODUCTION

Oxidative stress is defined as a disruption in the balance of reactive oxygen species production and antioxidant defenses (Betteridge, 2000). Free radicals derived from oxygen are classified as Reactive Oxygen Species (ROS), including superoxide radicals (O2-), hydroxyl radicals (OH +), and hydrogen peroxide radicals (H2O2). Enzymes that play a role in increasing the production of superoxide ions include the mitochondrial electron transport chain, NAD(P)H Oxidase, and Xanthine Oxidase. In the body, ROS is constantly being produced and eliminated, as long as the cell still has an endogenous defense against the oxidant. It is shown that low levels of ROS play a role in the physiology of normal cell signaling, or it is important to maintain homeostasis. Uncontrolled ROS production or failure ROS can be caused by oxidative stress, and several pathological abnormalities (Rush *et al*., 2005).

Oxidative stress causes oxidative failure to fats, proteins, and DNA (Asmat *et al*., 2016). ROS can cause a lipid peroxidation process that triggers various diseases agents, such as cancer, inflammation, atherosclerosis, and the aging process (Chen *et al*., 2018). Uncontrolled physical exercise is one of the factors producing oxidative stress (Ribeiro-Samora *et al*., 2017). Oxidative stress conditions also affect the hematological profile (Abdel-Moneim *et al*., 2019a), which is thought to be due to the release of inflammatory mediators (Boskabady and Farhadi, 2008). Aerobic exercise can increase oxygen consumption 10-20 times in the body and 100-200 times in skeletal muscle (Revan and Erol, 2011). Several recent investigations have found that NADPH oxidase enzymes in the skeletal play a signaling role in physiological responses to exercise and that they, together with xanthine oxidase enzymes, may contribute to the relative increase in whole-body oxidation (Jackson *et al*., 2016).

Antioxidants are compounds that can inhibit the process of free radical oxidation by donating an electron. In the body, antioxidants act as a defense mechanism against free radicals, some of them are naturally present in the body, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and glutathione-S-transferase (GST) (Sakr and Al-Amoudi, 2012; Sasongko *et al*., 2018). However, the increase of free radical formation due to external influences can make the defense system less effective so it requires the intake of antioxidants from the outside. Non-essential antioxidants such as α-tocopherol, β-carotene, vitamin C (Grażyna *et al*., 2017; Olale *et al*., 2019) and flavonoids can be obtained from various types of vegetables and fruits (Jiménez-Aguilar and Grusak, 2017).

***Corresponding author : Heru Sasongko**
Email : heru_sasongko@staff.uns.ac.id

Mangosteen (*Garcinia mangostana* L.) and mountain papaya (*Vasconcellea pubescens* A.DC.) are some types of plants that are often found in Indonesia (Sasongko *et al*., 2019). Mountain papaya is a typical plant of the Dieng plateau which has been known to contain flavonoid compounds that can be used as exogenous antioxidants. Mountain papaya extracts have IC50 of 0.983 - 1.2945 mg / 100 mL (Laily *et al*., 2012). Mangosteen rind contains various secondary metabolites such as xanthone, mangostin, tannin, and flavonoids (Im *et al*., 2017). These compounds are thought to play a role in determining the amount of antioxidants activity (Hassan *et al*., 2015). Innovations in oral antioxidants from natural products have been developed strongly in the future (Thomford *et al*., 2018). The use of a single extract is often considered to lack a strong effect (Sasongko *et al*., 2020). In natural products, extract mixes are used rather than separate components. At an equivalent dosage, crude plant extracts have been shown to have more activity than separated components (Rasoanaivo *et al*., 2011). In this study, a combination of mountain papaya and Garcinia mangostana ethanol extracts was investigated thought to have a synergistic effect as an antioxidant. Although not all combinations of substances have a synergistic impact.

METHODS

Materials

Mountain papaya fruits from Dieng plateu Wonosobo and mangosteen peel from Tawangmangu Karanganyar were used as samples test in this study. To confirm the validity of the plant, its sample was determined at the Faculty of Mathematics and Natural Sciences, Universitas Sebelas Maret. Wistar rats were obtained from the Faculty of Medicine*, Universitas Sebelas Maret Indonesia. Tris-HCl buffer solution, thiobarbiturate* (TBA), sodium decocyl sulfate, trichloroacetic acid (TCA) were gained from Sigma-Aldrich.

Extraction

Two kilograms dried of mountain papaya fruit and garcinia mangostana peel extracted by maceration method using ethanol 70% as solvent (1:3). The maceration process was carried out for 3 days then evaporated using a rotary evaporator at 50^0C until thick extract was obtained. The mountain papaya fruit extract (VPE) and garcinia mangostana peel extract (GME) were calculated as yield for the test (Sasongko *et al*., 2018).

Extract preparation

Mountain papaya fruit extract and garcinia mangostana peel extract are combined in three ratios. The single-dose was chosen based on previous studies' oxidative stress activity, which showed that garcinia mangostana peel extracts showed activity at a dose of 400 mg/kg (Arsana *et al*., 2013), and mountain papaya fruit extract at 240 mg/kg (Sasongko *et al*., 2018). Following the ratio between VPE: GME, which is 75:25; 50:50; and 25:75 in percent, the dosage ratio is split from a single dose based on literature.

In vivo experiment

The animal handling and experiments procedures were approved by the health research ethics committee of the Faculty of Medicine, Universitas Muhamadiyah Surakarta with the number 1809/A.1/ KEPK-FKUMS/I/ 2019. Twenty-five male rats were acclimatized for 7 days. Rats were divided into normal group, control group, and three combination extract doses. Based on a single successive dosage, the combinations of VPE and GME extracts were (60 mg/kg : 300 mg/kg), (120 mg/kg : 200 mg/kg), and (180 mg/kg : 100 mg/kg). The chronic exercise was done by swimming at 10 min/day for two weeks. Rats in the acute exercise groups were treated by swimming on the pail containing water (Arsana *et al*., 2013). Blood samples were collected from the orbital sinus to determine hematological parameters (Mai *et al*., 2017). The rats were then euthanized, and their livers were taken for evaluation of oxidative stress.

Measurement of hematological parameters

Blood taken from the rats was then given anticoagulants for analysis of the hematological profile. Measurement of hematologic parameters consisted of erythrocyte (RBC), hemoglobin (HGB), neutrophil (NEU), leukocyte (WBC), and lymphocyte (LYM) followed by Guder (Guder *et al*., 2014)

Malondialdehyde (MDA) and glutathione peroxidase (GPx) measurement

Five hundred milligrams of the liver were taken and added in 5 mL of 0.15 M Tris-HCl (pH 7.4) solution then homogenized by shaking it until 10% b/v homogenate was obtained. The thiobarbituric acid reactive substances (TBARS) technique was used to measure malondialdehyde using a UV-Vis spectrophotometer (Nurrochmad *et al*., 2013). Ellman's method of measuring

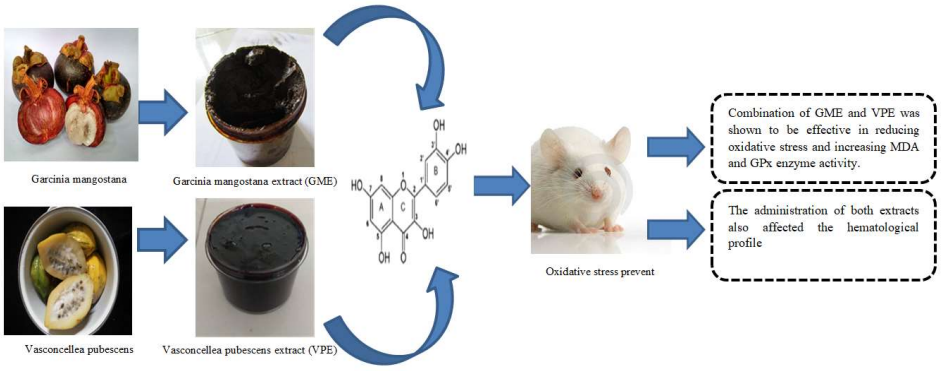

Figure 1. Graphical abstract

glutathione peroxidase levels is known as glutathione peroxidase level measurement (Ellman, 1959).

Statistical analysis

The stress oxidative and hematological data were collected to a one-way analysis of variance (ANOVA), supported by a Tukey HSD test post hoc to analyze the significant differences between groups at $p<0.05$. Subsequently, all data were proved as mean±standard deviation (SD).

RESULT AND DISCUSSION

Levels of MDA and GPx

The results showed that average MDA and GPx levels differ significantly ($p<0.05$) between treatments, as shown in Figures 2 and Figure 3. The results showed an increase in MDA levels in the control group, while the treated group also experienced an increase compared with normal rats. When compared to the control group, the levels of MDA in all extract combination groups were significantly different ($p<0.05$). The group of rats given a combination dose of GME and VPE with a ratio of 75:25 and 50:50 showed the same and significantly different reduction in MDA when compared to a dose of 25:75. Increased levels of MDA in the control group due to the production of free radicals caused by physical activity exceeds the body's antioxidant cellular defense resulting in oxidative stress (Jackson *et al*., 2016; Revan and Erol, 2011). As is known Malondialdehyde (MDA) is one of the results of lipid peroxidation caused by free radicals during maximum physical exercise or endurance training with high intensity (Tsikas, 2017). **G**lutathione peroxidase levels showed that the control rat group significantly decrease when compared to all other groups ($p<0.05$). The group of GME and VPE rats with a ratio of 75:25 and 50:50 showed no significant difference when compared with GPx levels of the normal group ($p>0.05$). This study shows that the group with a higher amount of GME produces a relatively better antioxidant effect. The findings of this study match with Chang *et al* (2020), a hypothesis that GME intake can reduce hepatic and muscle MDA levels. Exhaustive exercise resulted in higher MDA levels, according to this study. Endurance and high-intensity or exhausting activities result in oxidative stress and inflammation, which causes muscle fatigue and pain (Zheng *et al*., 2012). MDA levels in the liver have also been found to be higher after prolonged or severe exercise in previous investigations (Chang *et al*., 2020). After prolonged or severe exercise, xanthine oxidase (XO)-derived ROS, as well as mitochondrial-derived ROS, are major sources of ROS (Hellsten *et al*., 1997). The oxidation of hypoxanthine to xanthine is mediated by the xanthine oxidase (XO); the subsequent oxidation of xanthine to uric acid creates hydrogen peroxide, which is then removed by GPx and CAT by water conversion (Viña *et al*., 2000).

Measurement of hematological parameters

Table I shows the results of hematological profile measurements. Based on the hematological profile, it is known that the control group experienced an increase in WBC, LYM, and NEU values as well as a decrease in RBC and HGB values. When compared to the control group, the GME: VPE (75:25) group showed a significant difference in the LYM and NEU parameters. The GME: VPE (25:75) administration showed significant differences in all parameters besides the HGB value, and GME: VPE (50:50) dose showed no better change when compared to the control group. Administration of GME: VPE (75:25 and 25:75) showed a significant decrease when compared to the normal group. Oxidative stress can affect the increase of WBC, NEU, and decrease of RBC, HB, and HCT values (Abdel-Moneim *et al*., 2019a, 2019b). According to Sinaga and Zulaini's

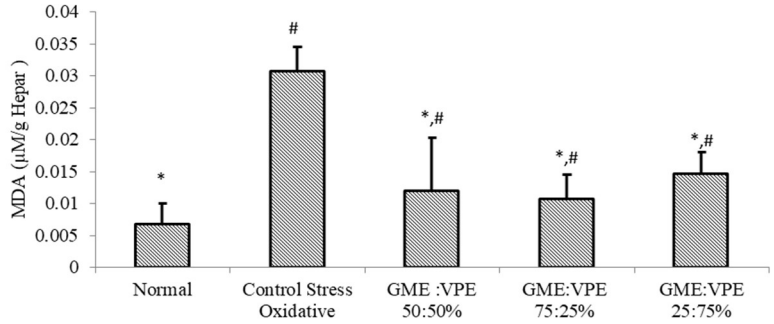

Figure 2. The effect of combination ethanol extract (GME-VPE) on MDA level. Symbols represent statistical significance : *p < 0.05, as compared to negative control group, #p < 0.05, as compared to normal group (n = 4/ group).

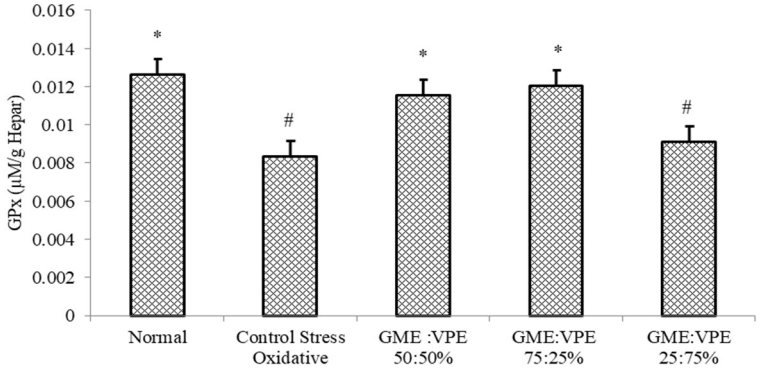

Figure 3. The effect of combination ethanol extract (GME-VPE) on GPx level. Symbols represent statistical significance : *p < 0.05, as compared to negative control group, #p < 0.05, as compared to normal group (n = 4/ group).

Table I. Hematological parameters following 14 days observation exposure of *Vasconcellea pubescens* A.DC and *Garcinia mangostana* Linn extract in mice

Groups	Normal	Control Stress Oxidative	GME: VPE (50:50)%	GME: VPE (75:25)%	GME: VPE (25:75)%
WBC (10^4xµL)	94.00 ± 6.08*	101.00 ± 21.7	172.33± 73.16	91.00 ± 6.08	81.33 ± 27.90*
RBC (10^4xµL)	779.33 ± 144.68*	626.67 ± 36.68	714.33± 64.22	619.67 ± 142.61#	744.33 ± 10.02*
HGB (g/dL)	12.50 ± 2.18	11.20 ± 0.87	13.20 ± 2.11	11.47 ± 3.23	12.53 ± 0.50
LYM (10^2xµL)	67.00 ± 19.31*	95.00 ± 19.29	108.50 ± 38.89	75.50 ± 23.33*	63.67 ± 22.68*
NEU (10^2xµL)	64.00 ± 26.00*	96.67 ± 11.2	100.00 ± 12.91	40.67 ± 10.80*#	17.67 ± 10.43*#

Symbols represent statistical significance: *p < 0.05, as compared to negative control group, #p < 0.05, as compared to normal group (n = 4/ group). WBC: White blood cell; RBC: Red blood cell; HGB: Hemoglobin; LYM: Lymphocyte; NEU: Neutrophile.

(2020) study, that giving mangosteen rind extract showed a decrease of LYM and NEU levels in rats given acute oxidative stress. Exercise-induced IL-6 release was linked to neutrophil mobilization and oxidative activity priming (Boskabady and Farhadi, 2008). Furthermore, IL-6 and adiponectin concentrations are thought to be the most effective agents in correcting WBC count (Johannsen *et al*., 2012). Repeated exposure to stress, on the other hand, can cause changes in the release rhythm as

well as sensitivity to the hormone glucocorticoids (Duclos *et al*., 2003). The increase in these hormones after acute and chronic exercise can cause other cells and tissues (blood monocytes) to become less sensitive to hormones or their receptors (e Silva *et al*., 2010).

Exercise causes the body to use more oxygen, which raises the formation of reactive oxygen species (ROS) and affects both enzymatic and non-enzymatic antioxidant defense mechanisms in target tissues and blood (Davies *et al*., 1982, Husain, 2003). Increased oxygen intake, catecholamine levels, lactic acid generation, raised rate of Hb auto-oxidation, and hyperthermia can all lead to an increase in ROS production during and after exercise (Osorio *et al*., 2003). Antioxidant intake prevented oxidative damage caused by intensive exercise (Belviranlı *et al*., 2012). Mountain papaya and mangosteen have flavonoid compounds that can act as exogenous antioxidants (Im *et al*., 2017, Sasongko *et al*., 2019). However, few research has looked at the effects of combining different types of extracts as antioxidants, and not all combinations provide a synergistic effect. This study showed a synergistic activity of mountain papaya and mangosteen, however more research needs to be done. Increasing the dosage of extract does not always result in an equal impact. The current study found that acute strenuous exercise resulted in oxidative stress and decreased antioxidant enzyme activity.

CONCLUSION

The combination of GME and VPE was shown to be effective in reducing oxidative stress and increasing MDA and GPx enzyme activity. Increasing the dosage of extract does not always result in an equal impact. Administration of GME and VPE also showed changes in the hematological profile. To be more complete, additional study with a longer exercise period and other blood biochemical markers is required.

REFERENCES

Abdel-Moneim, A., Mahmoud, B., Nabil, A., Negeem, Z., 2019a. Correlation between oxidative stress and hematological profile abnormalities in diabetic nephropathy. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13, 2365–2373.

Abdel-Moneim, A., Zanaty, M.I., El-Sayed, A., Khaled, R.G., Rahman, H.A., 2019b. Relation between oxidative stress and hematological abnormalities in children with type 1 diabetes. Canadian Journal of Diabetes.

Arsana, I., Adiputra, N., Pangkahila, J., Putra-Manuaba, I., 2013. Garcinia mangostana L. rind extract and physical training reduce oxidative stress in Wistar rats during maximal physical activity. Indonesian Journal of Biomedical Science 7, 63–68.

Asmat, U., Abad, K., Ismail, K., 2016. Diabetes mellitus and oxidative stress—A concise review. Saudi Pharmaceutical Journal 24, 547–553.

Belviranlı, M., Gökbel, H., Okudan, N., Başaralı, K., 2012. Effects of grape seed extract supplementation on exercise-induced oxidative stress in rats. British Journal of Nutrition 108, 249–256.

Betteridge, D.J., 2000. What is oxidative stress? Metabolism, Advances in Oxidative Stress Proceedings of an "Expert Session" held on the Occasion of the Annual Meeting of the European Association for the study of Diabetes 49, 3–8.

Boskabady, M.H., Farhadi, J., 2008. The possible prophylactic effect of Nigella sativa seed aqueous extract on respiratory symptoms and pulmonary function tests on chemical war victims: a randomized, double-blind, placebo-controlled trial. The Journal of Alternative and Complementary Medicine 14, 1137–1144.

Chang, C.-C., Chen, C.-W., Owaga, E., Lee, W.-T., Liu, T.-N., Hsieh, R.-H., 2020. Mangosteen Concentrate Drink Supplementation Promotes Antioxidant Status and Lactate Clearance in Rats after Exercise. Nutrients 12, 1447.

Chen, C.-Y., Kao, C.-L., Liu, C.-M., 2018. The Cancer Prevention, Anti-Inflammatory and Anti-Oxidation of Bioactive Phytochemicals Targeting the TLR4 Signaling Pathway. International Journal of Molecular Sciences 19, 2729.

Davies, K.J., Quintanilha, A.T., Brooks, G.A., Packer, L., 1982. Free radicals and tissue damage produced by exercise. Biochemical and biophysical research communications 107, 1198–1205.

Duclos, M., Gouarne, C., Bonnemaison, D., 2003. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. Journal of applied physiology 94, 869–875.

e Silva, T.S., Longui, C.A., Rocha, M.N., Faria, C.D.C., Melo, M.R., Faria, T.G., De Souza, J.A., Rizzo, L.V., 2010. Prolonged physical training decreases mRNA levels of glucocorticoid receptor and inflammatory genes. Hormone research in paediatrics 74, 6–14.

Ellman, G.L., 1959. Tissue sulfhydryl groups. Archives of biochemistry and biophysics 82, 70–77.

Grażyna, C., Hanna, C., Adam, A., Magdalena, B.M., 2017. Natural antioxidants in milk and dairy products. International Journal of Dairy Technology 70, 165–178.

Guder, W.G., Narayanan, S., Wisser, H., Zawta, B., 2014. Diagnostic Samples: From the Patient to the Laboratory: The Impact of Preanalytical Variables on the Quality of Laboratory Results. John Wiley & Sons.

Hassan, W., Zulkifli, R.M., Basar, N., Ahmad, F., Yunus, M.A.C., 2015. Antioxidant and tyrosinase inhibition activities of α-mangostin and Garcinia mangostana Linn. pericarp extracts. Journal of Applied Pharmaceutical Science 5, 037–040.

Hellsten, Y., Frandsen, U., Orthenblad, N., Sjødin, B., Richter, E., 1997. Xanthine oxidase in human skeletal muscle following eccentric exercise: a role in inflammation. The Journal of physiology 498, 239–248.

Husain, K., 2003. Interaction of exercise training and chronic NOS inhibition on blood pressure, heart rate, NO and antioxidants in plasma of rats. Pathophysiology 10, 47–56.

Im, A.-R., Im, A.-R., Kim, Y.-M., Kim, Y.-M., Chin, Y.-W., Chin, Y.-W., Chae, S., Chae, S., 2017. Protective effects of compounds from Garcinia mangostana L. (mangosteen) against UVB damage in HaCaT cells and hairless mice. International Journal of Molecular Medicine 40, 1941–1949.

Jackson, M.J., Vasilaki, A., McArdle, A., 2016. Cellular mechanisms underlying oxidative stress in human exercise. Free Radical Biology and Medicine, Human Performance and Redox Signaling in Health and Disease 98, 13–17.

Jiménez-Aguilar, D.M., Grusak, M.A., 2017. Minerals, vitamin C, phenolics, flavonoids and antioxidant activity of Amaranthus leafy vegetables. Journal of Food Composition and Analysis 58, 33–39.

Johannsen, N.M., Swift, D.L., Johnson, W.D., Dixit, V.D., Earnest, C.P., Blair, S.N., Church, T.S., 2012. Effect of different doses of aerobic exercise on total white blood cell (WBC) and WBC subfraction number in postmenopausal women: results from DREW. PloS one 7, e31319.

Laily, A.N., Suranto, S., Sugiyarto, S., 2012. Characterization of Carica pubescens in Dieng Plateau, Central Java based on morphological characters, antioxidant capacity, and protein banding pattern. Nusantara Bioscience 4.

Mai, A.S., dos Santos, A.B., Beber, L.C.C., Basso, R.D.B., Sulzbacher, L.M., Goettems-Fiorin, P.B., Frizzo, M.N., Rhoden, C.R., Ludwig, M.S., Heck, T.G., 2017. Exercise Training under Exposure to Low Levels of Fine Particulate Matter: Effects on Heart Oxidative Stress and Extra-to-Intracellular HSP70 Ratio. Oxidative Medicine and Cellular Longevity 2017, e9067875.

Nurrochmad, A., Margono, S.A., Sardjiman, Hakim, A.R., Ernawati, Kurniawati, E., Fatmawati, E., 2013. Hepatoprotective and antioxidant activity of pentagamavunon-0 against carbon tetrachloride-induced hepatic injury in rats. Asian Pacific Journal of Tropical Medicine 6, 438–442.

Olale, K., Walyambillah, W., Mohammed, S.A., Sila, A., Shepherd, K., 2019. FTIR-DRIFTS-based prediction of β-carotene, α-tocopherol and l-ascorbic acid in mango (Mangifera indica L.) fruit pulp. SN Appl. Sci. 1, 279.

Osorio, R., Christofani, J., D'almeida, V., Russo, A., Piçarro, I. da C., 2003. Reactive oxygen species in pregnant rats: effects of exercise and thermal stress. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 135, 89–95.

Rasoanaivo, P., Wright, C.W., Willcox, M.L., Gilbert, B., 2011. Whole plant extracts versus single compounds for the treatment of malaria: synergy and positive interactions. Malar J 10, S4.

Revan, S., Erol, A.E., 2011. Effects of endurance training on exhaustive exercise-induced oxidative stress markers. African Journal of Pharmacy and Pharmacology 5, 437–441.

Ribeiro-Samora, G.A., Rabelo, L.A., Ferreira, A.C.C., Favero, M., Guedes, G.S., Pereira, L.S.M., Parreira, V.F., Britto, R.R., Ribeiro-Samora, G.A., Rabelo, L.A., Ferreira, A.C.C., Favero, M., Guedes, G.S., Pereira, L.S.M., Parreira, V.F., Britto, R.R., 2017. Inflammation and oxidative stress in heart failure: effects of exercise intensity and duration. Brazilian Journal of Medical and Biological Research 50.

Rush, J.W.E., Denniss, S.G., Graham, D.A., 2005. Vascular Nitric Oxide and Oxidative Stress: Determinants of Endothelial Adaptations to Cardiovascular Disease and to Physical Activity. Can. J. Appl. Physiol. 30, 442–474.

Sakr, S.A., Al-Amoudi, W.M., 2012. Effect of leave extract of Ocimum basilicum on deltamethrin induced nephrotoxicity and

oxidative stress in albino rats. Journal of Applied Pharmaceutical Science 2, 22.

Sasongko, H., Efendi, N.R., Sugiyarto, 2018. The ethanolic extract of mountain papaya (Vasconcellea pubescens A.DC.) fruit against lipid peroxidation of rat liver tissues. AIP Conference Proceedings 2019, 050001.

Sasongko, H., Lestari, R., Yugatama, A., Farida, Y., Farida, Y., Farida, Y., 2020. Antidiabetic and Antioxidant Effect Combination Vasconcellea pubescens A.DC. and Momordica charantia L. Extract in Alloxan-Induced Diabetic Rats. Pharmacognosy Journal 12, 311–315.

Sasongko, H., Pratiwi, D., Amartiwi, T., Efendi, N.R., Sugiyarto, 2019. Hepatoprotective Effect of Mountain Papaya (Vasconcellea pubescens A.DC.) Fruit Extract against Acetaminophen-Induced Acute Liver Damage. Presented at the 1st Muhammadiyah International Conference on Health and Pharmaceutical Development, pp. 66–70.

Sinaga, R.N., Zulaini, Z., 2020. The Effect of Mangosteen Rind Extract (Garcinia mangostana L.) Toward Stress Oxidative Parameter, Leukocytes, Leukocytes Type Counts on Male Rats (Rattus norvegicus) with Excessive Physical Activity. Open Access Macedonian Journal of Medical Sciences 8, 904–909.

Thomford, N.E., Senthebane, D.A., Rowe, A., Munro, D., Seele, P., Maroyi, A., Dzobo, K., 2018. Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery. Int J Mol Sci 19, 1578.

Tsikas, D., 2017. Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges. Analytical Biochemistry, Lipid Methodology 524, 13–30.

Viña, J., Gimeno, A., Sastre, J., Desco, C., Asensi, M., Pallardó, F.V., Cuesta, A., Ferrero, J.A., Terada, L.S., Repine, J.E., 2000. Mechanism of free radical production in exhaustive exercise in humans and rats; role of xanthine oxidase and protection by allopurinol. IUBMB life 49, 539–544.

Zheng, X., Long, W., Liu, G., Zhang, X., Yang, X., 2012. Effect of seabuckthorn (Hippophae rhamnoides ssp. sinensis) leaf extract on the swimming endurance and exhaustive exercise-induced oxidative stress of rats. Journal of the Science of Food and Agriculture 92, 736–742.