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THE EFFECT OF RED DRAGON FRUIT PEEL EXTRACT ADMINISTRATION IN MICE *(Mus musculus)* ABSOLUTE MONOCYTE COUNTS IN PERIAPICAL RADIOGRAPHY EXPOSURE

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ABSTRACT
Background: *Exposure to periapical radiographic X-ray radiation can indirectly affect biological material which will trigger the formation of free radicals. An imbalance in the level of free radicals causes oxidative stress. To reduce it, additional antioxidants obtained from nature are needed. Natural antioxidants can be obtained from the peel of red dragon fruit which the function is to reduce the presence of free radicals.* ***Objective:*** *to analyze the effect of red dragon fruit peel extract administration in mice absolute monocyte counts in periapical radiographic exposure.* ***Method:*** *This study was a true experimental design with a post-test only with control group design. The research sample used 24 mice. Samples were divided into 6 groups: the control group was not given with the treatment, P1 to P4 group were given red dragon fruit peel extract at a dose of 100 mg / kg bb and exposed to radiation with different exposures, P5 group was given red dragon fruit peel extract but not exposed. P1 group was exposed to 1 dose (0.63 mGy), P2 group was exposed to 4 doses (1.66 mGy), P3 group was exposed to 8 doses (4.37 mGy), and P4 group was exposed to 12 doses (8.19 mGy).* ***Results:*** *This study showed that there were changes in the number of monocytes in all groups. The Games Howell test showed that the P1 group had a significant difference compared to the P4 and P5 groups.* ***Conclusion:*** *There is an effect of red dragon fruit peel extract administration in mice absolute monocyte counts in periapical radiographic exposure.*

Keywords: *Antioxidants, monocytes, periapical radiography, radiation, red dragon fruit peel.*
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INTRODUCTION

In dentistry, periapical radiography is the most common examination used by dentists before making a diagnosis, determining treatment plans, and evaluating treatment results. The dose of periapical radiography proposed by the *International Atomic Energy Agency* (IAEA) is 7 mGy.[1,2] One effect that can be caused by radiation is cell damage and inhibition of the formation and development of various types of blood cells, one of which is monocytes. Monocytes are a type of white blood cell that plays a role in cellular and humoral defense against foreign substances. Monocytes that are in the bloodstream are also known as Mononuclear Phagocyte System (MPS) which act to protect the body from the presence of organisms.[3,4] Leukocytes are a form of blood cells that have a major role in the immune system or kill microorganisms and germs that enter the human bloodstream. Leukocytes act as the first line of defense against microorganisms that are harmful to the body. Monocytes in human or rat blood are around 10% and 4%, respectively. The decreased number of monocytes can make a person vulnerable to various infections. One of the manifestations that appear in the oral cavity is the formation of ulcers in the oral mucosa. [5,6]

Exposure to ionizing radiation indirectly affects biological material that will form reactive species such as reactive oxygen species (ROS), reactive nitrogen species (RNS), and trigger free radicals. Free radicals are very reactive and can change biological structures such as DNA, proteins, and lipids. Oxidative stress occurs due to an imbalance of free radicals and antioxidants that affect cell damage in tissues. In principle, antioxidants act as radioprotectors. The way that can be done to reduce oxidative stress is to reduce exposure to free radicals and make the body's defense better by relying on antioxidant activity.[7,8]

Antioxidants are substances that can inhibit the oxidation process by binding to reactive free radicals and forming non-reactive free radicals so they will be stable when used to protect body cells from reactive oxygen free radicals. Based on the source, antioxidants are divided into endogenous antioxidants, antioxidant enzymes

produced by the human body itself, and exogenous antioxidants, which are obtained from outside the body / food. One example of exogenous antioxidants that can be obtained from nature is the peel of red dragon fruit (Hylocereus costaricensis). In previous studies, phytochemical tests showed red dragon fruit contains flavonoids, alkaloids, phenolics, tannins, vitamin C, saponins, terpenoids, and steroids.[8,9,10]

The results of a study conducted by Niah and Helda in (2016) who examined red dragon fruit peel extract with measurements using DPPH, found that the levels of antioxidants at a concentration of 0.0625; 0.125; 0.25; 0.5; and 1 gram / 100 mL and the ethanol content in dragon fruit peel extract can prevent the presence of free radicals that can harm the body. Research by Kristanto (2014) administered vitamin C which contains antioxidants in mice to study its effects on hemoglobin, leukocyte and platelet levels. This research shows that giving antioxidants to mice can increase the number of blood cells and prevent cell damage due to radiation exposure.[11,12]

Based on the background above, the researcher is interested to analyze the effect of antioxidant administration from red dragon fruit peel extract (Hylocereus costaricensis) on absolute monocyte counts in mice that exposed to periapical radiographic radiation with a single exposure dose of 0.63 mGy and a repeated dose of 1, 4, 8 and 12 times exposure.

MATERIAL AND METHODS

The study was conducted after obtaining ethical approval from the Faculty of Dentistry Research Ethics Commission, Lambung Mangkurat University No. 054 / KEPKG-FKGULM / EC / I / 2020. This study was a true experimental study using a post-test only with a control group design. The subject of the study was mice (Mus musculus) with criteria: male, age 3-4 months, body weight of 20-25 grams, and in good health and active. Mice were divided into 6 groups, the sample size of each group was 4 mice. The groups in this study were the control group and the treatment group.

Every treatment group was given 100 mg/kg BW red dragon fruit peel extract, but a different dose of radiation exposure. P1 group was given with 1 dose of radiation exposure (0.63 mGy), P2 group with 4 times of the radiation exposure dose (1.66 mGy), P3 group with 8 times the dose (4.37 mGy), P4 group with 12 times (8.19 mGy), and P5 group without radiation exposure.

Red Dragon Fruit Peel Extraction

Red dragon fruit was obtained from the red dragon fruit plantation, Bajuin, Tanah Laut. Red dragon fruit was taken as many as 7 kg and separated between the pulp and rind. 3 kg red dragon fruit peel sample, which has been separated from the flesh, carried out a wet sorting process. Furthermore, the peel of the red dragon fruit was cut into small sizes by 0.5 mm. After that, the slices were dried for 3-4 days in the sun and followed by using an oven at 55 ° C for 24 hours. The peel of dried red dragon fruit is macerated using 70% ethanol solvent. The ethanol solvent was poured into a maceration container filled with the sample while stirred until it was evenly distributed. Extraction was carried out for 3 x 24 hours and every 24 hours the liquid was replaced while stirred occasionally. The extracted filtrate was evaporated until a thick extract was obtained, called a liquid ethanol extract, and was subsequently evaporated using a rotary evaporator at a temperature of $50^{o} – 70^{o}$ C. Furthermore, the extract was thickened using a water bath to obtain a thick extract of red dragon fruit peels.[11]

Administering Extracts in Mice

A thick extract of red dragon fruit peel was made into a solution by dissolving 100 mg/kg BW. 20-25 grams mouse required a 2-2.5 mg extract dissolved in 0.5 ml distilled water, according to the volume of the mouse's stomach. The extract was given using gastric sonde for 6 days, so that antioxidants can be distributed to the tissues. X-ray Irradiation on Periapical Radiography.

X-ray Irradiation on Periapical Radiography

On the 6th day, all groups of mice in the study were then taken to the Dental Radiology Section of Gusti Hasan Aman Dental Hospital for irradiation. Transport of mice from the Kalimantan Polytechnic Pharmaceutical Laboratory leading to Gusti Hasan Aman Dental Hospital was carried out by car. To facilitate the process of radiation exposure, mice were placed in a box-shaped cage made of wire, with styrofoam to hold the mice from moving. At the bottom of the box, a dosimeter was placed to measure the dose of radiation absorbed by mice. In the group of mice with repeated exposure, each exposure was given a break of 1 minute before the next exposure to adjust the situation.

Blood Sampling

Blood samples were taken 24 hours after radiation. Before blood was drawn, mice were given inhalation anesthesia according to the CCAC Experimental Care and Use Guidelines (2020). The advantage of inhalation anesthesia is minimal detoxification by the body, because it is inhaled into the lungs, and the dose can be controlled easily and quickly. The mice were put into a covered jar filled with cotton with diethyl ether to anesthetize the mice, then waited until the mice did not move or die. Next, the mice were dissected by cutting the mice's abdomen skin and opening the inside of the stomach using crooked scissors until the heart was visible. Then the syringe was inserted into the heart and 1 ml of blood was suctioned using a 1 ml disposable syringe 26 G x 1/2 inch. Blood samples for each mouse were stored in a vaculab containing EDTA so that the blood did not clot when transferred. The monocyte counting was then performed using the blood smear method.[13,14]

RESULT

Absorbed dose based on dosimeters in the experimental group as follows:

Table 1. The average dose of periapical radiographic radiation absorbed by mice

Group	Periapical radiographic radiation	Average dose of exposure (mGy)
P1	1 time	0,63
P2	4 times	1,66
P3	8 times	4,37
P4	12 times	8,19

Table 1 shows the average radiation dose absorbed by mice with 1, 4, 8, 12 times periapical radiographic radiation exposure. According to the IAEA, the recommended reference dose limit for periapical radiography is 7 mGy. In table 1, group P1 with 1 time of exposure, the absorbed radiation dose was 0.63 mGy, group P2 with 4 times exposure was 1.66 mGy, and group P3 with 8 times exposure was 8.19 mGy. The data shows that the radiation dose absorbed by mice is still below the reference dose according to the IAEA. In the P4 group with 12 exposures, the radiation dose absorbed by mice was 8.19 mGy. This indicates that the dose absorbed by mice has exceeded the reference dose.

Table 2. Mean and Standard Deviation of absolute monocyte counts (AMC) in male mice exposed to periapical radiographs and administered with red dragon fruit peel extract

Group	N	Mean ± SD Scoring
P1	4	8.6250 ± 4.34687
P2	4	9.2325 ± 3.48245
P3	4	47.5100 ± 38.87714
P4	4	23.6250 ± 5.11125
P5	4	13.2725 ± 9.14537
K	4	10.0900 ± 6.75849

Note: P1: 1 exposure; P2: 4 times the exposure; P3: 8 times the exposure; P4: 12 times exposure; P5: given extract and without radiation exposure; K: control.

Table 2 shows the mean of monocytes counts in all groups. P1 group with 1 exposure, the mean of monocyte counts was 8,6250 cells / mm^3 with an SD score of 8,6250. P2 group with 4 times exposure, the mean of monocyte counts was 9.2325 cells / mm^3 with SD score 3.48245. P3 group with 8 times exposure, the mean of monocyte counts was 47,5100 cells / mm^3 with an SD score of 38.87714. In the P4 group with 12 episodes, the mean of monocyte counts was 23,650 cells / mm^3 with an SD score of 5.11125. Group P5 was extracted but not exposed, the mean of monocyte counts was 13.2725 cells/ mm^3 with an SD score of 9,14537. The mean of monocyte counts in the control group was 10,0900 cells/ mm^3 with an SD score of 6.75849.

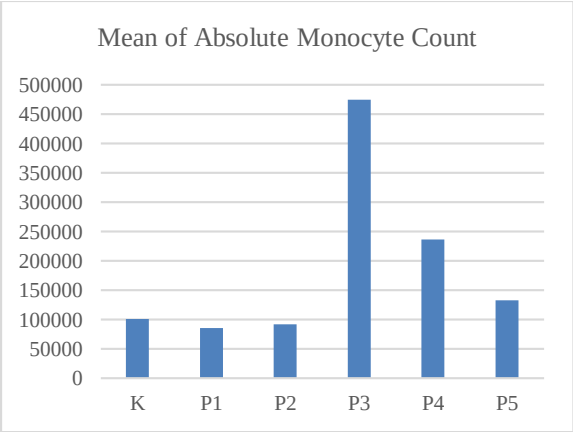

Figure 1. The Absolute Monocyte Count of Mice

Figure 1 shows that the monocyte counts in the P3 group mice revealed a higher growth in the monocyte counts than the other groups. The P4 group also showed an increase in the monocyte counts, but the P3 group was still higher. The P1 and P2 groups exposed to radiography and given a 100 mg/kg BW red dragon fruit peel extract showed a decrease in the monocyte counts compared to the control group, but the monocyte counts in the P2 group was higher than P1. The P5 group without radiation exposure was significantly higher than the control group, but the monocyte counts in the P4 group was still higher than the P5 group.

Table 3. Shapiro Wilk Data Normality Test

Group	N	Sig.
K	4	0.085
P1	4	0.082
P2	4	0.276
P3	4	0.352
P4	4	0.802
P5	4	0.819

The results of normality test of monocyte counts in mice using Shapiro-wilk showed a value of p> 0.05 which means the data was normally distributed. Then the data analysis continued with homogeneity test using Levene's Test.

Table 4. Levene's Test Homogeneity Test

Levene's Test Homogeneity	
Monocyte counts	Sig.
Based on mean	0.000

The Homogeneity test using Levene's Test shows the distribution of non-homogeneous data with a value of p = 0,000 (p <0.05). Data analysis continued with the One-Way ANOVA test with a confidence level of 95% to find out significant differences between treatment groups.

Table 5. ANOVA Statistical Analysis Results

ANOVA				
	Sum of Square	df	F	Sig.
Counts	9689.671	23	3.248	0.029

Tabel 6. The Games Howell Test influences periapical radiographic radiation exposure by administration of red dragon fruit peel extract to the absolute number of monocytes in male mice (*Mus musculus*).

	K	P1	P2	P3	P4	P5
K	-	.999	1	.523	.125	.990
P1	.999	-	1	.492	.032*	.924
P2	1	1	-	.503	.032*	.947
P3	.523	.492	.503	-	.811	.594
P4	.125	.032*	.032*	.811	-	.462
P5	.990	.924	.947	.594	.462	-

Note: *) significantly different

Data analysis using Games Howell Test aims to find out which groups have significant differences. The P1 group had a significant difference compared to the P4 group, the value of p = 0.032 and the P2 group was significant to the P4 group, the value of p = 0.032, which means the value of p<0.05.

Morphological description of monocyte cells with Giemsa staining can be seen in the figure. 2.

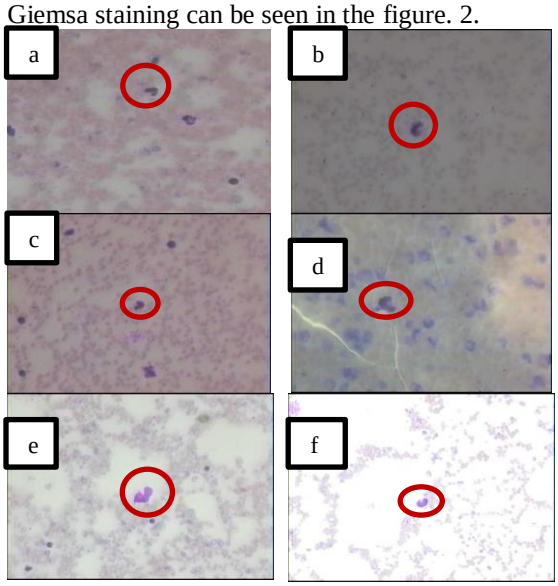

Figure 2. Morphological depiction of monocytes by Giemsa staining, horseshoe-shaped or oval shaped monocyte cells. a). P1 group with 1 exposure, b). P2 group with 4 times exposure, c). P3 group with 8 times the exposure, d). P4 group with 12 times exposure, e). Group with administered extract and without exposure, f). Control group.

DISCUSSION

This research shows that there is an effect of red dragon fruit peel extract administration in mice absolute monocyte counts in periapical radiography radiation exposure. Groups that showed a significant increase in absolute monocyte counts were in the treatment group administered with red dragon fruit peel extract and exposed to 8 times and 12 times radiation exposure. In this study, the control group is a group that did not receive any treatment. Whereas the P5 group was the group that administered with red dragon fruit peel extract at a dose of 100 mg/kg without exposure to radiation. Groups P1 to P4 were administered red dragon fruit peel extract and exposed to radiation with different doses. Group P1 and P2 showed a slight decrease when compared to group P5. P3 group exposed to 8 times the radiation showed a significant increase compared to P1 and P2 groups.

Group P5 showed a slight increase when compared to the control group. This can be caused by the effect of giving red dragon fruit peel extract which has antioxidant activity. The composition of compounds in the peel of red dragon fruit are flavonoids, vitamin C, tannins, alkaloids, steroids, and saponins. Antioxidants contained in the peel of red dragon fruit acts as an immunomodulator. Immunomodulators are ingredients used to enhance the body's immune repair system. The nature of immunomodulators consists of immune stimulators, immune restorators, and immune supressors that can change the activity of the body's immune system. The general mechanism of immune stimulation is to help

to correct the immune system imbalance by increasing specific or non-specific immunity.[15,16]

According to research from Pasaribu (2015), extracts that contain lots of flavonoids can activate the lymph to increase monocyte production so that it can increase the number of monocytes. Another study by Kurniawati (2018) using purple leaf extract showed that administration of extracts containing flavonoids and alkaloids could increase the production of proinflammatory cytokines so as to increase endocytosis and phagocytosis by monocytes.[17,18]

P3 group had the highest number of monocytes among all experimental groups. Group P3 was given with red dragon fruit peel extract and exposed 8 times with a mean dose of 4.37 mGy. This can occur because the radiation dose in the P3 group approaches the reference dose by the IAEA, resulting in a lot of damage in the tissue. Radiation, as one of the physical factors causing inflammation, can trigger an inflammatory response due to cell damage in tissue. Photons from radiation can hit cells and cause changes in cell molecules and can indirectly trigger the formation of free radicals because of the lysis of water molecules.[22] This mechanism causes cell injury which then induces macrophages and monocytes in the circulation, then expresses M-CSF to multiply monocytes and tissue migration. The function of monocytes after differentiating into macrophages which perform phagocytosis is to digest dead cell particles. Increased M-CSF will induce monocyte formation and macrophage proliferation. Circulating monocytes will migrate to the tissue and turn into M2 macrophages which play a role in tissue repair. Polarization of anti-inflammatory M2 macrophages is mediated by STAT-3 and STAT-6 signaling in response to IL-4 and IL-13 with the involvement of IRF-3 and IRF-4. On monocytes, IRF-3 prevents pro-inflammatory polarization for M1 macrophages while IRF-4 promotes the anti-inflammatory M2 phenotype.[19,20,21]

Damage that occurs in DNA cells (Deoxyribonuclei Acid) caused by exposure to x-ray radiation will cause apoptosis that is controlled by the p53 gene in the cell cycle. Cell death caused by radiation releases inflammatory mediator products that will induce the release of monocytes and differentiation of macrophages by M-CSF.[22] Monocytes that migrate to tissues then turn into phenotypic M2 macrophages in response to anti-inflammatory signals that are responsible for overcoming inflammation and encouraging tissue repair.[23,21] Cell death can occur due to indirect effects of radiation that will form free radical compounds. If free radicals and antioxidant compounds are not balanced, it will cause oxidative stress. Protein, which plays a role in cell repair, is damaged by excessive doses. If in the self-repair mechanism these cells are damaged, cells do not have the ability to differentiate and apoptosis occurs.[4,24,25]

The P4 group showed a slightly lower monocyte counts than the P3 group. This can be caused by radiation doses that have exceeded the reference dose. In group P4, the mean of absorbed dose was 8.19 mGy. This causes most of the monocytes in the circulation and the bone marrow to be damaged or death, so the number of monocytes released into circulation is slightly lower than the P3 group. The decrease in the monocyte counts in the treated group was due to high doses of periapical radiographic radiation that would cause cell death as a biological effect of x-ray radiation. Repeated radiation exposure will cause DNA damage.[4,24]

Groups P1 and P2 had slightly lower monocyte counts than P5 which was not exposed to radiation. This may occur because the administrator of extracts to mice 1 time and 4 times the radiation exposure causes increase the activity of macrophages. The number of monocytes decreases because they have differentiated into macrophages. Macrophage differentiation is influenced by two main cytokines, namely G-CSF and M-CSF. M-CSF-induced cells are more involved in tissue repair and release of IL-10 anti-inflammatory cytokines. In this case, inflammation that occurs due to radiation exposure is related to clearance by M2 macrophages which the differentiation is influenced by M-CSF cytokines.[16,21]

As for this research, there are deficiencies that are not entirely in accordance with the actual situation. This study only measured the number of monocytes in mice after treatment and did not consider the condition before the treatment, so the range of the radiation exposure effect remains unknown. The addition of anticoagulants in blood samples can cause lysis of cells resulting in the number of cells in the sample tends to be lower so that the examined blood sample is not fully in line with the actual situation. In this study, it can be concluded that there is an effect of red dragon fruit peel extract administration in mice (*Mus musculus*) absolute monocyte counts in periapical radiography radiation exposure.

REFERENCES

1. Prasetya AN, Prasetyarini S, Sulistiyani. Perubahan Apoptosis Sel Asinar Kelenjar Parotis Akibat Pajanan Radiasi Sinar-X Dosis Rendah. e-Jurnal Pustaka Kesehatan. 2018. p.1-7.
2. Azorin C, Azorin J, Aguirre F, Rivera T. Dose Measurements in Intraoral Radiography using Thermoluminescent dosimeters. Journal of Physics. 2015; 582(2015): 1-2.
3. Hayati K, Astuti ER, Martini T. Aktivitas Superoksida Dismutase, Katalase dan Kadar Malondialdehida Kelenjar Submandibularis Tikus Wistar Setelah Iradiasi Sinar Gamma. Jurnal Syiah Kuala Dent Soe. 2016; 1(2): 110-121.
4. Ardiny K, Supriyadi, Subiyantoro S. Jumlah Sel pada Isolat Monosit Setelah Paparan Tunggal Radiasi Sinar X dari Radiografi Periapikal. e-Jurnal Pustaka Kesehatan. 2014; 2(3): 563-569.
5. Wacleche V.S., et al. The Biology of Monocytes and Dendritic Cells: Contribution to HIV Pathogenesis. Journal Viruses. 2018; 10(65): 1-31.

6. Rafika M, Wahyuni I.S, Hidayat W. Penentuan Laju Alir Saliva Pada Pasien Geriatri Sebgai Pertimbangan Manajemen Komprehensif Pada Stomatitis Herpetika. Jurnal B-Dent. 2018; 5(2): 144-152.
7. Darlina, Rahardjo T dan Syaifudin M. Evaluasi Hubungan Dosis Radiasi Terhadap Kerusakan Dna Sel Limfosit Dengan Menggunakan Tes Comet. Indonesian Journal of Nuclear Science and Technology. 2018; 19(1): 13-20.
8. Khaira K,. Menangkal Radikal Bebas dengan Anti-oksidan. Jurnal Sainstek. 2010; 2(2): 183-186.
9. Werdhasari A. Peran Antioksidan Bagi Kesehatan. Jurnal Biotek Medisiana Indonesia. 2014; 3(2): 59-68.
10. Laurencia E, Tjandra O. Identifikasi senyawa kimia ekstrak metanol buah naga merah (Hylocereus polyrhiz) dengan kromatografi gas. Tarumanagara Medical Journal. 2018; 1(1): 67-73.
11. Niah R dan Helda. Aktivitas Antioksidan Ekstrak Etanol Kulit Buah Naga Merah Daerah Pelaihari, Kalimantan Selatan Dengan Metode DPPH (2,2-difenil-1-pikrilhidrazil). Jurnal Pharmascience. Oktober 2016; 3(2): 36 - 42.
12. Kristanto, dan Daniel. Berkebun Buah Naga. Jakarta: Penebar Swadaya. 2014. p.20-21.
13. Canadian Counsil On Animal Care. Guide to the Care and Use of Experimental Animal Vol 1 2nd Edition. Ottawa, Ontorio; 2020. p.134-135.
14. Restel TI, Porfiriol LC, de Sauza AS, Silva IS. Hematology of Swiss mice (Mus musculus) of both genders and different ages. Acta Cirurgica Brasileira. 2014; 29(5): 306-312.
15. Rahman H, Aldi Y, Mayanti E. Aktivitas Imunomodulator dan Jumlah sel Leukosit dari Ekstrak Kulit Buah Naga Merah (Hylocereus lemairei (Hook.) Britton & Rose) pada Mencit Putih Jantan. Jurnal Farmasi Higea. 2016; 8(1): 44-57.
16. Listiani N, Susilawati Y. Potensi Tumbuhan Sebagai Imunostimulan. Farmaka. 2019; 17(2): 222-231.
17. Pasaribu W, Longdong S.N.J, Mudeng J.P. Efektivitas Ekstrak Daun Pacar Air (Impatiens balsamina L.) Untuk Meningkatkan Respon Imun Non Spesifik Ikan Nila (Oreochromis niloticus). Jurnal Budidaya Perairan. 2015; 3(1): 83-92.
18. Kurniawati A. Pengaruh Ekstrak Etanol Daun Ungu (EEDU) Graptophyllum Pictum L. Griff terhadap Aktivitas Fagositosis Monosit yang dipapar Candida Albicans. Denta Jurnal Kedokteran Gigi. 2018; 12(1): 126-133.
19. Mills C.D, Lenz L.L, Ley K. Macrophages at the Fork in the Road to Health or Disease. Frontiers in Immunology. 2015; 6(59): 1-6.
20. Adenin I. Peran Komponen Inflamasi Akibat Insersi Alat Kontrasepsi dalam Rahim dan Hubungannya dengan Peningkatan Kadar Glikodelin A. eJKI. 2019; 7(2): 156-161.
21. Orekhov A.N, et al. Monocyte Differentiation and Macrophage Polarization. Vessel Plus. 2019; 3(10): 1-20.
22. Ajani N, Sukmana BI, Erlita I. Pengaruh Sinar Radiasi Terhadap Kalsium Saliva Pada Radiografer di Banjarmasin. Jurnal Kedokteran Gigi Dentin. 2019; 3(1): 29-34.
23. Sari L.M. Apoptosis: Molecular Mechanisms of Cellular Death. Jurnal Cakradonya Dent J. 2018; 10(2): 65-70.
24. Hasan I, Djakaria .H.M. Kematian Sel Akibat Radiasi. Journal of The Indonesian Radiation Oncology Society. 2013; 4(2): 39-77.
25. Arief H dan Widodo M.A. Peranan Stres Oksidatif Pada Proses Peyembuhan Luka. Jurnal Ilmiah Kedokteran Wijaya Kusuma. 2018; 5(2): 22-29.