The Role of Macrofags In Pregnant Rats With Chronic Periodontitis as A Risk of Preeclampsia

by Ardhiyan Rahmadi

Submission date: 23-Mar-2022 11:57AM (UTC+0800)
Submission ID: 1790679857
File name: nt_Rats_With_Chronic_Periodontitis_as_A_Risk_of_Preeclampsia.pdf (151.12K)
Word count: 3643
Character count: 19391

DocID: https://connectjournals.com/03896.2020.20.4865

Biochem. Cell. Arch. Vol. 20, No. 2, pp. 4865-4869, 2020 | www.connectjournals.com/bca | *ISSN 0972-5075*

THE ROLE OF MACROFAGS IN PREGNANT RATS WITH CHRONIC PERIODONTITIS AS A RISK OF PREECLAMSIA

Ardhiyan Rahmadi[1], Anita Yuliati[2] and Pratiwi Soesilawati[3]*

[1]Graduate Student of Dental Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Dental Material, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3]Department of Oral Biology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
*e-mail: pratiwi-s@fkg.unair.ac.id

(Received 3 July 2020, Revised 21 September 2020, Accepted 26 September 2020)

ABSTRACT : Periodontitis is an inflammatory disease of tooth supporting tissue caused by specific microorganisms, one of which is the bacteria *Porphyromonas gingivalis* (*P. gingivalis*). Based on the Basic Health Research (RISKESDAS) in 2018, dental and mouth problems reached 57.6% in Indonesia and only 10.2% had received services from medical personnel. In pregnancy there are hormonal changes that can affect periodontal tissue. Increasing the number of macrophages in pregnancies with chronic periodontitis can lead to a risk of preeclampsia. The aim of this study is toprove that pregnant mice with chronic periodontitis can increase the number of macrophages as a risk of pre-eclampsia. Thirty females *Rattus novergicus*, weighing 250-300 g with age 5-6 months, divided into 3 groups, consisting of 1 control group and 2 treatment groups. The control group is only pregnant mice. In treatment group 1 is the group of pregnant rats with chronic periodontitis and in treatment group 2 is the group of rats with chronic periodontitis. *P. gingivalis* ATCC 33277 was injected locally 0.03ml with a concentration of $1x10^9$ CFU / ml under the incisor gingival sulcus in the right and left mesials. Data on the number of macrophages were analyzed using Kolmogorov-Smirnov and One-Way Anova. There were significant differences in the mean number of macrophages between groups. There is an increase in macrophages in pregnant mice with chronic periodontitis

Key words : Macrophages, preeclampsia, maternal health, chronic periodontitis.

INTRODUCTION

Periodontitis is one of the most common diseases in humans, which is an inflammatory disease of dental support tissue caused by specific microorganisms *Porphyromonas gingivalis* (*P. gingivalis*) is a gram-negative anaerobic bacteria in the oral cavity, which is a major cause of peridontal disease (Rafiei *et al*, 2017; Nugraha *et al*, 2020). Based on the Basic Health Research (RISKESDAS) in 2018, dental and mouth problems reached 57.6% in Indonesia and only 10.2% had received services from medical personnel (Riskesdas, 2018). Periodontitis does not only cause oral dysfunction but is also associated with systemic pathology and has been considered a risk factor for cardiovascular disease, peripheral arterial disease, respiratory disease and low birth weight (Arigbede *et al*, 2013; Han *et al*, 2018; Newman *et al*, 2014).

Periodontitis is described as a potential risk that can increase complications in pregnancy. Periodontal disease occurs in 20% to 50% of pregnant women (Sgolastra *et al*, 2013). In pregnant women hormonal changes occur which will trigger the body's response to infection. The most common manifestation in the oral cavity in pregnant women is pregnancy gingivitis and it has been reported that almost 100% occur in pregnant women. This occurs because of an increase in estrogen and progesterone which causes an increase in vascularity and vascular flow along with changes in the immune system (Martina *et al*, 2007). During the process of pregnancy there will be physiological and psychological changes. Changes that occur during pregnancy can affect several parts of the body including the oral cavity especially in the periodontal tissue which is caused by an increase in the levels of the hormones progesterone and estrogen, which can affect small blood vessels of the gingiva, periodontal ligament and alveolar bone (Özen *et al*, 2012; Nareswari *et al*, 2019; Hisham *et al*, 2019). Preeclampsia is followed by an increase in proinflammatory mediators namely Interleukin-6 (IL-6), Tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) and a decrease in Interleukin-10 (IL-10) (Xie *et al*, 2011). Then the bacteria enter the placenta and will increase the inflammatory

response in the fetal placenta. Damage to the placenta will disrupt blood flow from the mother and fetus so that it affects the blood pressure of the mother and causes preeclampsia (Bobetsis *et al*, 2014; Dörtbudak *et al*, 2005; Lang and Lindhe, 2015; Raghupathy, 2013; Sowmya *et al*, 2015).

Preeclampsia is a disorder that occurs in pregnant women accompanied by an increase in systolic blood pressure of more than 140 mmHg and diastolic more than 90 mmHg and proteinuria more than 300 mg/dl. Preeclampsia can cause maternal and fetal morbidity and morbidity. Preeclampsia is a pregnancy-specific syndrome with decreased organ perfusion, which results in vasospasm of the blood vessels and endothelial activation. As many as 3.9% of all pregnant women in the world experience preeclampsia (Cunningham, 2009).

In periodontitis, lipopolysaccharides from the bacterium *P. gingivalis* enter the systemic through the bloodstream thereby triggering systemic inflammation (Sowmya *et al*, 2015). In chronic periodontitis, monocytes and macrorags are activated by *P. gingivalis* bacterial endotoxins and are followed by the appearance of inflammatory mediators such as interleukin-1â (IL-1â). interleukin-6 (IL-6), interleukin-7 / (IL-7), interleukin-23 (IL-23), Tumor Necrosis Factor-α (TNF-α), matrix metalloproteinase (MMP-8) and (MMP-8) 9) in gingival crevicular fluid (GCF). The presence of lipopolysaccharides in the bloodstream causes the body to respond by activating proinflammatory cytokines. In this situation the production of proinflammatory cytokines becomes more and there is an acute phase response in the liver which causes an increase in CRP (C-Reactive Protein) (Ren, 2017).

In preeclampsia, there is an increase in proinflammatory cytokines and a decrease in anti-inflammatory cytokines such as IL-10. IL-10 plays a role in the immune response to inhibit the production of various proinflammatory cytokines. Polymorphism of the promoter IL-10 causes a decrease in IL-10 production, this is related to the occurrence of preeclampsia (Sowmya *et al*, 2015). High levels of proinflammatory cytokines in pregnant women with periodontitis can result in trophoblast apoptosis, causing failure of trophoblast invasion and followed by placental ischemia. Trophoblast apoptosis can also cause uterine contractions so that it can cause premature birth (Bauer *et al*, 2004; Bobetsis *et al*, 2014; Monzón-Bordonaba *et al*, 2002).

Based on the above data, we will examine the amounts of macrophages in pregnant mice with chronic periodontitis as a risk of preeclampsia.

MATERIALS AND METHODS

In this study used 30 female wistar rats aged 5-6 months with weights ranging from 250-300 grams and adapted for 7 days according to the method of Llyod *et al* (2003) and Hardy *et al* (2004). Age selection is based on the fact that the size of the jaws and gingiva of rats at an age large enough to be applied with drugs. Female and male mice were placed in separate cages. Wistar rats eat the same brand and are replaced every day. Try animals placed in a cage that is far from noise. Each enclosure is labeled in the form of a group name. The mat of the cage is given husk and replaced every two days, given a place of food and the bottle ends with a pipe for straw as a place to drink rats (Hardy *et al*, 2004; Lloyd *et al*, 2004).

This study was divided into 3 groups, consisting of 1 control group and 2 treatment groups. The control group was only a group of pregnant rats. The treatment group 1 is the group of pregnant rats with chronic periodontitis and the treatment group 2 is the group of rats with chronic periodontitis.

Female wistar mice were injected with the hormone Pregnant Mare Serum Gonadotropin (PMSG) and human Chrionic gonadotropin (hCG) to stimulate superovulation. Then the female wistar rat was injected 10 IU PMSG intraperitoneally, 48 hours later the same rat was injected 10 IU hCG intraperitoneally. After injection, female and male wistar rats were put in one cage in a ratio of 1: 1 for one night. The next day, a vaginal plug was checked for female wistar rats. If there is a vaginal plug, then it is determined as the 0th day of pregnancy (Liu *et al*, 2013)

Periodontitis treatment is carried out in pregnant and nonpregnant mice. In pregnant mice, periodontitis treatment is carried out on the 7th day of pregnancy. In mice that are not pregnant, periodontitis treatment is carried out one day after the rat adaptation. Female mice were given 0.03 ml Pophorymonas gingivalis ATCC 337 ml locally with a concentration of 1 x 109 CFU / ml under the gingival sulcus of their left and right mesial incisors. The same procedure is then repeated every three days for two weeks. Chronic periodontitis can occur after 10 days of injection of Pophorymonas gingivalis in mice (Krismariono, 2016).

Female wistar rats in each group I, II, and III were decaputated after 2 weeks of exposure to *Pophorymonas gingivalis*. In pregnant mice that is at the end of pregnancy the 21st day. Decaputation is done by first anesthetizing the mouse intra-muscularly using ketamine. Rat periodontal tissue was taken for further histopathological examination. Macrophage cell count

calculation using Hematoxylin Eosin staining and examination preparations under a microscope.

RESULTS

Blood pressure measurement is done one day before euthanasia. T

Proteuria measurements were carried out on the 20th day. P1 group has high blood pressure and very high proteinuria, which can be interpreted as mice experiencing preeclampsia.

Data normality test results for the number of macrophages in all three groups, sig. in column P all values p> 0.05 are obtained. So it can be said that all data obtained are normally distributed.

It is known that the results of Oneway ANOVA data processing showed a p-value in the macrophage group of 0,000, this value is smaller than the significance level a <0.05, meaning that there are significant differences in the macrophage group.

To strengthen the results of the One Way ANOVA test, and to ascertain which pairs of groups are different, proceed with the Post Hoc Test and as a result it can be seen in Table 2.

Based on Table 2, the significance value (Sig.) of the Macrophage variable in each group is known to be 0,000. Because all Sig. <0.05, it can be concluded that there are significant differences in the mean number of macrophages between groups.

DISCUSSION

Chronic periodontitis is a multifactorial infectious disease that occurs due to an association between the immune response with periodontal pathogenic bacteria. Chronic periodontitis is characterized by periodontal tissue loss over a period of time. Chronic periodontitis can be caused by poor oral hygiene, which causes a buildup of biofilms. In addition, chronic periodontitis can also be caused by systemic and environmental factors that can change the immune response in biofilms so that they can develop progressively (Agrali and Kuru, 2015).

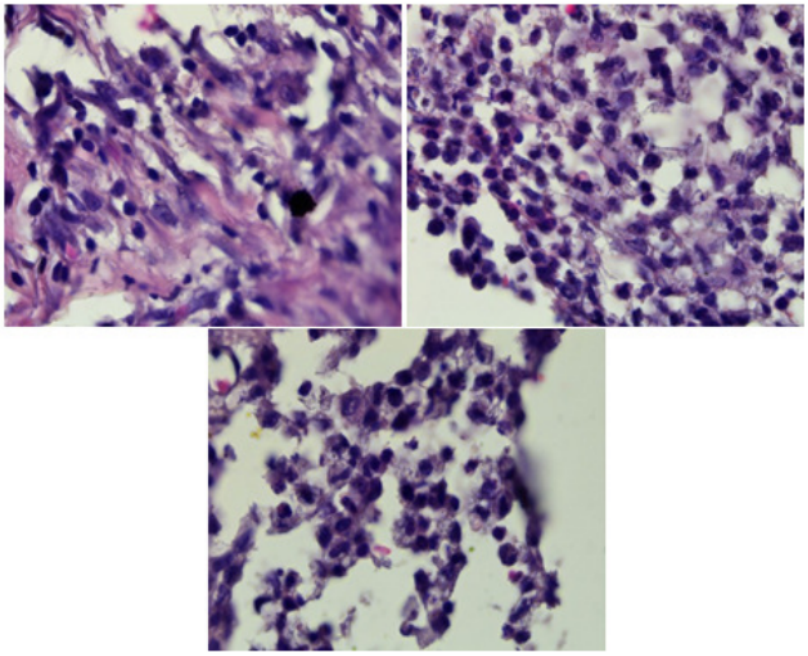

Fig. 1 : Histology H&E staining 400x magnification shows macrophage in K group (a), P1 group (b) and P2 group (c).

This study aims to look at the symptoms of preeclampsia in chronic periodontitis in the form of increased blood pressure, proteinuria, the number of macrophages conducted in female wistar rats. Increased blood pressure and proteinuria are a sign of preeclampsia. Preeclampsia is an increase in blood pressure> 140/90 mmHg that occurs after 20 weeks' gestation accompanied by proteinuria> 300 mmHg on examination of the carikel in a random sample of urine permanently. Proteinuria is an objective marker, which shows the occurrence of extensive endothelial leakage, which is a characteristic of preeclampsia (Cunningham, 2009).

In this study, there were three groups consisting of one control group namely negative control (K-) and two

Table 1 : Kolmogorov Smirnov test results on the number of chronic inflammatory cells of macrophages.

Cell Type	Group	N	Mean	P
Makrofag	P1	10	16,8	0,589
	P2	10	10,3	0,383
	K-	10	4,5	0,335

Table 2 : The results of the Post Hoc Test statistical analysis of the number of macrophage chronic inflammatory cells.

	P1	P2	K-
P1	-	0,000	0,000
P2	0,000	-	0,000
K-	0,000	0,000	-

treatment groups namely Treatment 1 (P1) and Treatment 2 (P2). The control group consisted of a negative control group ie pregnant with no periodontitis. The treatment group consisted of treatment group 1 namely pregnant periodontitis and treatment group 2 namely non-pregnant periodontitis.

Mutual effects of periodontal diseases are possible factors adjusting progression of systemic diseases. Macrophages are fundamental cells for the inflammation as controller guiding inflammation to chronic inflamation. Macrophages are elaborate in a curiously of homeostatic developments of the host. In the immunity path, macrophages are known as ubiquitous mediators of cellular turnover and maintenance of extracellular matrix homeostasis (Hasturk *et al,* 2012; Narmada *et al*,2019; Yuliati *et al*, 2019).

P. gingivalis, as an oral pathogen contributing to the chronic inflammatory lesions of periodontitis, would induce an M1 polarized macrophage population. This type of macrophage is primarily associated with inflammatory responses to bacterial infections, and is a primary cell type for combatting these infections. a collateral aspect of the induction of M1 cells, particularly through engagement of TLRs, is signaling through the INF-yB pathway and production of an array of proinflammatory mediators. While it is clear that inflammation is required as a presage to the development of adaptive immunity, chronic elevated levels of these biomolecules in the local tissues is associated with undermining epithelium integrity, enzymatic degradation of connective tissue matrix and loss of fibroblast function/viability, and activation of osteoclastogenesis leading to alveolar bone resorption. *P. gingivalis* clearly has the ability to trigger this pathway in macrophages and synergizes with host factors, i.e. IFN³ and extrinsic LPS to induce significant elevations in M1-produced inflammatory mediators (Huang *et al*, 2016; Soesilawati *et al*, 2019).

In the treatment group 2 non-pregnant periodontitis rats had a blood pressure increase that was not too high compared to other groups. In treatment group 1 namely pregnancy and periodontitis there was an increase in blood pressure because the bacteria that caused periodontitis would release endotoxies in the form of LPS and enter the systemic. Proinflammatory mediators can be measured by activating the acute phase response in the liver by stimulating an increase in CRP production at plasma levels. Increased production of excess CRP results in inhibited endothelial nitric oxide synthase (eNOS) synthesis, so that NO production decreases and endothelin-1 (ET-1) increases. The imbalance between NO and ET-1 results in increased shear stress so that it can cause endothelial dysfunction which can cause hypertension (Khaleel Jameel and Rajiv Joshi, 2015).

In this study, the results of proteinuria measurements were obtained, it was known that an increase in the amount of proteinuria on day 14 and day 20 in treatment group 1 was pregnant mice with periodontitis. An increase in the amount of proteinuria occurs because in endothelial dysfunction, renal arteriolar vasospasm occurs, namely narrowing of the arteries resulting in intrinsic damage to the glomerular membrane. Glomerular membrane damage to proteins resulting in leakage and decreased glomerular filtration, this condition will cause proteinuria. This shows that in the first treatment group pregnant periodontitis experienced preeclampsia which was characterized by high blood pressure and high proteinuria (Suwanti *et al*, 2014; Uzan *et al*, 2011).

CONCLUSION

Based on the results of the study, it can be concluded that an increase in macrophages in pregnant mice with chronic periodontitis can increase the risk of preeclampsia.

REFERENCES

Agrali O B and Kuru B E (2015) Periodontal treatment in a generalized severe chronic periodontitis patient: A case report with 7-year follow-up. *European J. Dent.* **9**(2), 288-292.

Arigbede A, Babatope Bo and Bamidele M K (2013) Periodontitis and systemic diseases: A literature review. *J. Indian Society of Periodontol*. **16**(4), 487.

Bauer S, Pollheimer J, Hartmann J, Husslein P, Aplin J D and Knöfler M (2004) Tumor Necrosis Factor-α Inhibits Trophoblast Migration through Elevation of Plasminogen Activator Inhibitor-1 in First-Trimester Villous Explant Cultures. *J. Clin. Endocrinology and Metabolism* **89**(2), 812–822.

Bobetsis Y A, Barros S P and Offenbacher S (2014) Exploring the relationship between periodontal disease and pregnancy complications. *The J. American Dental Association* **137**, S7–S13.

Cunningham G F (2009) Fisiologi Ibu Hamil. In *Obstetri Williams*.

Dörtbudak O, Eberhardt R, Ulm M and Persson G R (2005)

Periodontitis, a marker of risk in pregnancy for preterm birth. *J. Clin. Periodontol*. **32**(1), 45–52.

Han Y K, Jin Y, Miao Y B, Shi T and Lin X P (2018) Improved RANKL production by memory B cells: A way for B cells promote alveolar bone destruction during periodontitis. *Int. Immunopharmacol*. **64**(36), 232–237.

Hardy C M, Clydesdale G and Mobbs K J (2004) Development of mouse-specific contraceptive vaccines: infertility in mice immunized with peptide and polyepitope antigens. *Reproduction* **128**(4), 395–407.

Hasturk H, Kantarci A and Van Dyke T E (2012) Oral inflammatory diseases and systemic inflammation: role of the macrophage. *Frontiers in Immunol*. **3**,118.

Hisham P B B M, Narmada I B, Alida A, Rahmawati D, Nugraha A P and Putranti N A (2019) Effects of Vitamin D in Alveolar Bone Remodeling on Osteoblast Numbers and Bone Alkaline Phosphatase Expression in Pregnant Rats During Orthodontic Tooth Movement. *J. Orofac. Sci.* **11**, 79-83.

Huang C B, Alimova Y and Ebersole J L (2016) Macrophage polarization in response to oral commensals and pathogens. *Pathogens and Disease*, 74(3).

Khaleel Jameel M and Rajiv Joshi A (2015) Effect of acute stress on serum cortisol level in female wistar rats. *Int. J. Healthcare and Biomedical Res*. **3**(4), 109-113.

Krismariono A (2016) The decreasing of NFêB level in gingival junctional epithelium of rat exposed to Porphyromonas gingivalis with application of 1% curcumin on gingival sulcus. *Dental J. (Majalah Kedokteran Gigi)* **48**(1), 35.

Lang N P and Lindhe J (2015) Clinical periodontology and implant dentistry. Volume **1***/ : Basic concepts*.

Liu N, Zhou C, Chen Y and Zhao J (2013) The involvement of osteopontin and â3 integrin in implantation and endometrial receptivity in an early mouse pregnancy model. *Europ. J. Obstetrics Gynecology and Reproductive Biol.* **170**(1), 171–176.

Lloyd M L, ShellamG R, Papadimitriou J M and Lawson M A (2004) Immunocontraception is Induced in BALB/c Mice Inoculated With Murine Cytomegalovirus Expressing Mouse *Zona pellucida* 31. *Biol. Reprod.* **68**(6), 2024–2032.

Martín-Coello J, González R, Crespo C, Gomendio M and Roldan E R S (2008) Superovulation and *in vitro* oocyte maturation in three species of mice (*Mus musculus*, *Mus spretus* and *Mus spicilegus*). *Theriogenology* **70**(6), 1004-1013.

Monzón-Bordonaba F, Vadillo-Ortega F and Feinberg R F (2002) Modulation of trophoblast function by tumor necrosis factor-α: A role in pregnancy establishment and maintenance? *Am. J. Obstetrics and Gynecol.* **187**(6), 1574-1580.

Nareswari R A A R, Narmada I B, Djaharu'ddin I, Rahmawati D, Putranti N A and Nugraha A P (2019) Effect of vitamin D administration on vascular endothelial growth factor expression and angiogenesis number in orthodontic tooth movement of pregnant Wistar rats. *J Postgrad Med Inst.* **33**(3), 182-188.

Narmada I B, Husodo K R D, Ardani I G A W, Rahmawati D, Nugraha A P and Iskandar R P D (2019) Effect of Vitamin D during Orthodontic Tooth Movement on Receptor Activator of Nuclear Factor Kappa-B Ligand Expression and Osteoclast Number in Pregnant Wistar Rat (*Rattus novergicus*) **8**(1), 38-42.

Newman M G, Takei H H and Klokkevold P R (2014) Carranza's Clinical Periodontology. 11th Edition. In *J. Chem. Information and Modeling*.

Nugraha A P, Rezkita F, Puspitaningrum M S, Luthfimaidah M S, Narmada I B, Prahasanti C, Ernawati D S and Rantam F A (2020) Gingival Mesenchymal Stem Cells and Chitosan Scaffold to Accelerate Alveolar Bone Remodelling in Periodontitis: A Narrative Review. *Research J. Pharm. and Tech.* **13**(5), 2502-2506.

Özen B, Özer L, Ba°ak F, Altun C and Açikel C (2012) Turkish women's self-reported knowledge and behavior towards oral health during pregnancy. *Medical Principles and Practice* **21**(4), 318–322.

Rafiei M, Kiani F, Sayehmiri F, Sayehmiri K, Sheikhi A and Azodi M Z (2017) Study of Porphyromonas gingivalis in periodontal diseases: A systematic review and meta-analysis. *Medical J. Islamic Republic of Iran* **31**(1), 355–362.

Raghupathy R (2013) Cytokines as key players in the pathophysiology of preeclampsia. *Medical Principles and Practice* **22**(Supp. 1), 8–19.

Ren H (2017) *Role of Maternal Periodontitis in Preterm Birth*. **8**(February), 1–10.

Riskesdas (2018) *Hasil Utama Riskesdas 2018*. Jakarta: Kementrian Kesehatan Republik Indonesia, 1–100.

Sgolastra F, Petrucci A, Severino M, Gatto R and Monaco A (2013) Relationship between periodontitis and pre-eclampsia: a meta-analysis. *PloS One* **8**(8), 24–26.

Soesilawati P, Ambarani E L and Oki A S (2019) Increased vascular endothelial growth factor (VEGF) expression in Wistar rat oral mucosa traumatic ulcer due to Golden Sea Cucumber (*Stichopus hermanni*) extract gel. *Acta Medica Philippina,* **53**(6).

Sowmya S, Ramaiah A, Nallari P, Jyothy A and Venkateshwari A (2015) Role of IL-6 –174(G/C) promoter polymorphism in the etiology of early-onset preeclampsia. *Inflammation Res.* **64**(6), 433–439.

Suwanti, Wibowo E and Safitri N A (2014) Hubungan tekanan darah dan paritas dengan kejadian eklampsia di ruang bersalin RSUP NTB tahun 2012. *Media Bina Ilmiah* **8**(1), 25-30.

Yuliati T K, Rananda I and Soesilawati P (2020) Increasing macrophages in tooth extraction wound healing after induction of freeze-drying gel *Aloe vera* 90% on *Cavia cobaya. Mal. J. Med. Health Sci.* **16**(Supl.4), 87-91.

Xie C, Yao M Z, Liu J B and Xiong L K (2011) A meta-analysis of tumor necrosis factor-alpha, interleukin-6 and interleukin-10 in preeclampsia. *Cytokine* **56**(3), 550-559.

The Role of Macrofags In Pregnant Rats With Chronic Periodontitis as A Risk of Preeclampsia

ORIGINALITY REPORT

18%	15%	12%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.e3s-conferences.org Internet Source	1%
2	www.scilit.net Internet Source	1%
3	repository.unair.ac.id Internet Source	1%
4	www.ncbi.nlm.nih.gov Internet Source	1%
5	news.unair.ac.id Internet Source	1%
6	www.jove.com Internet Source	1%
7	ourarchive.otago.ac.nz Internet Source	1%
8	www.jidmr.com Internet Source	1%
9	connectjournals.com Internet Source	1%

10	"Preeclampsia", Springer Nature, 2018 Publication	1 %
11	V Sutanti, D Fuadiyah, LH Hidayat, T Agnizarridlo, K S Anggiarta. "Analysis of the effect of extracted yellow kepok banana peels (Musa paradisiaca l.) on the size and morphology of Enterococcus faecalis", Journal of Physics: Conference Series, 2020 Publication	1 %
12	eprints.ummi.ac.id Internet Source	1 %
13	journal.unpad.ac.id Internet Source	1 %
14	journals.sagepub.com Internet Source	1 %
15	Sosmitha Girisa, Aviral Kumar, Varsha Rana, Dey Parama et al. "From Simple Mouth Cavities to Complex Oral Mucosal Disorders—Curcuminoids as a Promising Therapeutic Approach", ACS Pharmacology & Translational Science, 2021 Publication	1 %
16	revistas.uautonoma.cl Internet Source	<1 %
17	Bo Yang, Xuefei Pang, Zhipeng Li, Zhuofan Chen, Yan Wang. "Immunomodulation in the	<1 %

Treatment of Periodontitis: Progress and Perspectives", Frontiers in Immunology, 2021
Publication

18	docplayer.com.br Internet Source	<1 %
19	journal.unj.ac.id Internet Source	<1 %
20	Eduardo R. S. Roldan, Toshitaka Horiuchi, Ryuzo Yanagimachi. "Superovulation in immature and mature Chinese hamsters", Gamete Research, 1987 Publication	<1 %
21	jofs.in Internet Source	<1 %
22	www.frontiersin.org Internet Source	<1 %
23	Ninuk Hariyani, Anisa Nur Halimah, Mohammed Al-Junaid, Oki Fadhila, Theresia Indah Budhy. "Mouse Periodontitis Models Using Whole Porphyromonas gingivalis Bacteria Induction", The Saudi Dental Journal, 2021 Publication	<1 %
24	Opeyemi Oluwafemi Ojueromi, Ganiyu Oboh, Ayokunle Ademosun. "Effect of Black Seeds (Nigella sativa) on Inflammatory and Immunomodulatory Markers in Plasmodium	<1 %

berghei-Infected Mice", Research Square Platform LLC, 2022
Publication

25	journal-denta.hangtuah.ac.id Internet Source	<1%
26	mafiadoc.com Internet Source	<1%
27	"Clinical Cases in Dental Hygiene", Wiley, 2018 Publication	<1%
28	Farkhan Atoillah, Sri Hartini. "Design of Sustainable Value Stream Mapping to Improve the Sustainability Indicator: Case in MDF Company", Journal of Physics: Conference Series, 2021 Publication	<1%
29	Jorge Hernán Ramirez, Roger Arce, Adolfo Contreras. "Why Must Physicians Know About Oral Diseases?", Teaching and Learning in Medicine, 2010 Publication	<1%
30	Park, Hae-Ryung, and Rita Loch-Caruso. "Protective effect of nuclear factor E2-related factor 2 on inflammatory cytokine response to brominated diphenyl ether-47 in the HTR-8/SVneo human first trimester extravillous trophoblast cell line", Toxicology and Applied Pharmacology, 2014. Publication	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

The Role of Macrofags In Pregnant Rats With Chronic Periodontitis as A Risk of Preeclampsia

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5