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Foreword

Honourable fellow scholars and distinguished guests,

On behalf of the Indonesian academics and researchers in the UK, I would like to thank the organising committee for inviting us to be the Board of Reviewers for the ISIC 2015 conference. I have personally been following the development of the ISIC-TIIMI network for the last five years and I am proud to witness that the network is growing from strength to strength. The variety of the programme has been tremendously increased; showing endless new ideas emerging from the organisation committee.

The theme of this year's conference is very much aligned with the strategic vision of the government of the Republic of Indonesia to continue the development of our nation to progress towards eradication of poverty and corruptions, safeguarded by a stable economy and a caring society. In this respect, I noticed that this year's conference has attracted a large number of submissions of scientific papers that both directly and indirectly support our government's programme, demonstrating great interests and passion amongst the authors.

The ISIC conference offers a great avenue for research training. As part of the exercise, I am very pleased that the board of reviewers have played an important role in maintaining the reputation of the conference by ensuring that the papers have undergone a scientific and thorough review process, akin to an International conference. This should ultimately warrant not only the quality of the accepted papers but also the potential impacts the papers might have. Whether your paper is accepted or not, I hope you can learn from the constructive feedback given by the reviewers.

Those who are invited to present their papers at King's College should be proud of yourselves. This is an exciting time for you to disseminate your work at one of the UK's premiere universities. I therefore strongly encourage you to learn from the feedback or comments you might receive, and take the advantage of the network of both Indonesian and non-Indonesian scholars in the UK, be they students, academic staff, researchers or others who have distinguished career outside academia. There is no doubt that the ISIC conference will give you a valuable experience and will expand your horizon.

Finally, I hope you have a productive meeting and enjoy the beginning of autumn in London.

Dr Benny Tjahjono
Head of the Board of Reviewers
ISIC conference 2015

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EFFECTS OF *Pediococcus pentosaceus* BACTERIA ISOLATED FROM *DADIH* TO THE LEVEL OF TNF-α ON THE INFLAMMATORY PERIODONTAL TISSUE INDUCED BY *Porphyromonas gingivalis* BACTERIA

EXPERIMENTAL RESEARCH LABORATORY AT *Sprague - dawley* RAT

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ABSTRACT

Introduction : The primary aetiology of periodontal disease, one of which is irritation of specific pathogens which will produce lipopolysaccharide toxins. These toxins will trigger the production of tumour necroting factor alpha (TNF-α) whom the high productivity can lead to bone resorbtion. The purpose of this study was to determine the effects of the *Pediococcus pentosaceus* bacteria which were isolated from *dadih* to the amount of TNF-α in rat periodontal tissue inflammation induced by bacteria *Porphyromonas gingivalis*. **Method** :The study was conducted on 27 Sprague Dawley Rats consists of 3 treatment groups. Examination of TNF-α was conducted by using Enzyme-Linked Immune Sorbent Assay (ELISA). **Results** :The result of ANOVA statistical test was $p = 0.01$ where $p < 0.05$ means that all treatment groups had significant differences. **Conclusion**: *Dadih* can reduce the amount of TNF-α in periodontal tissue inflammation.

Keywords : Periodontal tissue inflammation, *Porphyromonas gingivalis, Pediococcus pentosaceus*

I. INTRODUCTION

Periodontal disease is a disease with a high rate of complaints. The number of the worldwide adult population who suffer from periodontal disease is about 50% (Wahyukundari, 2009). The primary aetiology of periodontal disease is irritation of specific pathogens (Charles, 2008). The secondary aetiology is poor condition of mouth cavity, smoking, education level, socioeconomic status, age, pregnancy, genetic factors and systemic disease (Widyastuti, 2009). Specific pathogens that have the ability to penetrate and damage the periodontal tissue are *Porphyromonas gingivalis* which have the most rapid growth at the time of periodontitis. In normal conditions, the amount of bacteria was only 10.6, while at the time of periodontitis, the number had risen into 59.5 (Fauziah and Herawati 2008, Carranza and Camargo 2006). *Porphyromonas gingivalis* will remove lipopolysaccharide toxins (LPS), after that this toxin will induce cellular events which are the beginning of the protection mechanisms of the innate immune system. Next, phagocytic cells such as polymorphonuclear neutrophils, monocytes and macrophages trigger the release of chemical mediators such as cytokines. Cytokine Cells that play a role in periodontal disease are: Interleukin -1

(IL - 1), Interleukin - 6 (IL-6), tumour necrosis factor-α (TNF-α) and Interferon - gamma (IFN-γ) (Amin *et al. 2010,* Eley *et al. 2010).*

The inflammation can increase osteoplastic processes that result in bone resorption. The TNF-α activity can improve the function of osteoclast genesis and reduce the function of many osteoblast genesis (Boyce *et al. 2005).* Many resorptions are mediated by the increased local production of pro-inflammatory cytokines such as TNF-α. (TNF-α can stimulate bone resorption by: (1) inducing the proliferation and differentiation of osteoclast progenitors and activate the osteoclast formation indirectly, (2) stimulating collagenase and degradation of type I collagen by fibroblasts that trigger tissue destruction periodonsium (Erica *et al.* 2000*).* By looking at the effects of the high level activity of TNF-α, we need a medication that can inhibit or reduce the activity of TNF-α in inflammatory conditions.

Today, the treatment of periodontitis is continuously being developed by one of them is using probiotics. Probiotic is defined as living microorganism, specifically bacteria that is safe to be consumed by human and will give benefit for human if it is consumed in adequate amount. The definition has been approved by UN through FAO and WHO (Bonifait *et al.* 2009). One of the traditional probiotics that many people are consumed is *dadih*. *Dadih* is a homemade probiotic done by the people of West Sumatera which originated from fermented buffalo milk in a bamboo tube by lactic acid-producing microorganism which are naturally found in the buffalo milk. *Dadih* has Lactic Acid Bacteria (LAB) which are different in each region and can be identified by using 16S rRNA. LAB are a big cluster of beneficial bacteria which has relatively common characteristics (Purwanti *et al.* 2011). The study of Purwanti (2010) found that in buffalo milk *dadih* dominated by the *Lactococcus* bacteria, *Pediococcus pentosaceus*, *Enterococcus faecalis* and *Weisella*. One product of lactic acid bacteria is nisin. Nisin is a natural antibiotic that has bacteriocins and the widest activity of spectrum (Yuliawati *et al.* 2012). The nisin can make the *dadih* -isolated bacteria prevent further inflammation caused by pathogens in periodontal disease. *Pediococcus pentosaceus* is typical of *dadih* -isolated pathogen in West Sumatra which is now known to have the ability to inhibit the growth of gram-positive bacteria and gram-negative.

Figure 1 *Dadih* (Source : Purwanti *et al.* 2011)

II. RESEARCH METHOD

This study has received ethical permission which was from the Research Ethics Committee of the Faculty of Medicine, University of Andalas No: 006/KEP/FK/2015. The purpose of this study is to determine the effect of *Pediococcus pentosaceus* bacteria which were isolated from *dadih* to the level of TNF-α in rat periodontal tissue inflammation induced by bacteria *Porphyromonas gingivalis*. This study is an experimental laboratory study conducted at the Laboratory of Livestock Product Technology Faculty of Animal Science, Biomedical Laboratory and animal house of Faculty of Medicine, University of Andalas from January to April 2015. The samples in this study were 27 male Wistar divided into three groups. Group 1 was the negative control group which was not given any

treatment, group 2 was the positive control group which was given *Porphyromonas gingivalis* bacteria for 15 days, group 3 was given treatment groups by *Porphyromonas gingivalis* bacteria for 15 days and *Pediococcus pentosaceus* bacteria for 5 days.

Materials used for this study are: 27 male Wistar rats, *Porphyromonas gingivalis* bacteria, *Pediococcus pentosaceus* bacteria isolated from *dadih* , the liquid of de Monitol ROGOSA Salt Broth (MRS-B), the liquid of de Monitol Media ROGOSA Salt Agar (MRS-A), Brain Heart Infusion Agar (BHI - A), Brain Heart Infusion Broth (BHI - B), Yeast Extract, Hemin, Vitamin K, chloroform, Phosphate Buffer Saline, Alcohol, distilled sterile, liquid spritus, sterile cotton, filter paper, standard drinks and food for wistar rats, Preenrichment, aluminum foil, Washing Buffer.

The tools used for this study are: Anaerobic jar, Eppendrof, serum separator tube, Magnetic striter, Hockey sticks, lamp spritus, Lamina flow, Quebec Colony Counter, Cage + a place to eat and drink for Wistar rats, Syringe size 30G, test tube, petridish, ohaus balance, Incubator, Autoclave, measuring cup, flask, glass beaker, Ose, Lamp spritus, Vibrator, Stopwatch, Stove, Pots, Gloves, masks, Refrigerators, eBioscience ELISA Kit with catalogue number 88-7340, Micro plate reader set, Spectrophotometer.

Treatment procedure was done by the injection of *Porphyromonas gingivalis* bacteria in the positive control and treatment group. The injection was performed at the junctional epithelium of the upper molar teeth left at a dose of 0.5 ml. Before the treatment, rats were anaesthetized beforehand by using chloroform. Procedures of injecting *Pediococcus pentosaceus* bacteria isolated from *dadih* were applied via sublingual administration for 5 days. The dose was about 1 cc/treatment with a total minimal of bacteria colonies was about 2 x 10^8 cfu/ml. Blood sampling procedure for inspection of TNF-α is taken from the rat aorta and the amount of the blood sample was 1 cc. After that, the serum was separated and had TNF-α tested by using ELISA.

Figure 2 Procedure of research

III. RESULT

The data analysis was done by using ANOVA test. The data normality test was done previously by using Shapiro Wilk, while the homogeneity test was performed by using Lavene test. The data results had data normality test performed by using test of normality Shapiro Wilk. Shapiro Wilk test results showed abnormal data, hence data transformation must be done first. The data transformation showed that all data normally distributed. Levene homogeneity test showed that all of the data have the same variance.

Table 1 The Results of TNF-α level in the 3 groups

	TNF-α Level ng/ml	
	n	x ± SD
Negative control group	7	0,22 ± 0,11
Positive control group	7	0,32 ± 0,29
Treatment group	7	0,06 ± 0,01

Homogeneity test and Levene test were qualified for the Anova test. One way ANOVA test showed p = 0.01 where p <0.05 means that all treatment groups had significant differences. After the ANOVA results obtained, then the Least Significant Difference (LSD) test was performed to determine the differences of average level of TNF-α in each group.

Table 2 LSD Test

Treatment group	Comparison	P
Negative Control	Positive Control Treatment	0,555
		0,002*
Positive Control	Negative Control	0,555
	Treatment	0,001*
Treatment	Positive Control	0,001*
	Negative Control	0,002*

LSD test results showed that there were significant differences between the treatment, positive control and negative control (P <0.005) and there was no significant difference between the positive control and negative control (P> 0.005).

IV. DISCUSSION

Periodontal disease is a common infection that requires serious mouth cavity health care. Periodontal disease is associated with infection of gram-negative bacteria. Gram-negative may release endotoxin to perform repeat infection in the host, which usually starts from the edge of the gingival sulcus, and gradually to the deeper parts, including the destruction of the periodontal ligament and bone alveolar. Therefore, it is necessary to do a research on changes of periodontal tissue inflammatory (Liao *et al.* 2013). The study nowadays is using rats as a research model.

This study used the induction method of *Porphyromonas gingivalis* bacteria to make periodontal tissues of rat become inflammatory. The induction was performed in the positive control group and the treatment group during the first 15 days in the first molar of left upper jaw of rats. After

15 days of induction, the rat negative control and positive control group had their blood drawn and checked the level of TNF-α from each group. Blood sampling were originally done in the lingual veins, yet it was cancelled due to the amount minimum of blood from the lingual vein, based on this reference, the blood sampling is done from a vein aorta.

Scans showed that the negative control group had an average value of 0.22 ± 0.11 ng/ml while the positive control group had an average value of 0.32 ± 0.29 ng/ml. There was increasing level in the TNF-α level of negative control group which is associated with increased levels of stress rats at the time of blood sampling where negative controls had never given any treatment before. This is in line with a research conducted by Madrigal *et al.* (2002) regarding increased levels of TNF-α after given a stress exposure which results in an increase of the level of TNF-α in cortex after 1 hour stress induced. This incident was preceded by an increase in TNF converter (TACE) in the cortex of the brain after 30 minutes of exposure to stress. One of the weaknesses of TNF-α test is there is no specific inflammatory source of an increase in TNF-α, so further research is needed for more specific information. No significant difference between the negative control and positive control could be due to the increased time of proinflammatory cytokines in acute condition occurred not long after followed by increasing anti-inflammatory cytokines. Hence, these conditions need to be considered if the researchers want to assess the level of cytokines that appear during inflammation.

The positive control group also experienced an increase in TNF-α caused by the induction of *Porphyromonas gingivalis* bacteria. The elevated levels of proinflammatory cytokines in periodontal tissues is in line with a research conducted by Molon *et al.* (2014). regarding the variation of the response of rat which were induced by periodontal disease where the group of *Porphyromonas gingivalis* bacteria-induced ATCC 33 277 had their expression pro-inflammatory cytokines increasing on 15th examination day. An increase in pro-inflammatory cytokines is consistent with a research conducted by Mysak *et al.* (2013). One of the gram-negative bacteria in the periodontal disease is *Porphyromonas gingivalis*. One of its activities is to generate lipopolysaccharide endotoxin which is a major factor in the progression of periodontal disease. Moreover, gingival fibroblasts are the major connective tissue gingival which can directly interact with *Porphyromonas gingivalis* and its products such as lipopolysaccharide. Lipopolysaccharide can activate an inflammatory reaction in the host which may be a sign for the hosts that the infection was happening. One form of inflammatory response is cytokines generating. One of high cytokines at the time of the periodontal infection is TNF-α.

Clinical signs which appear in the mouth cavity of rat which occurs in the positive control and treatment group on day 7 is area-induced gums had red colour and swollen if it is compared with the other side. Moreover, the reddish colour clearly visible when the effect of the anaesthetics chloroform already started to disappear in rat. Redness and swelling in the same area is in line with the research observed by Nitawati *et al.* (2014). In the study, redness, swelling and bleeding started on day 2 post-induction of *Porphyromonas gingivalis* bacteria.

After periodontal inflammation was induced during 15 days, the treatment group was given the probiotic bacteria originating from *dadih* s-isolated *Pedicoccus pentosaceus* bacteria for 5 days after blood sampling was done and the level of TNF-α in this group has been checked. Test results showed the treatment group had an average value of 0.06 ± 0.05 ng/ml. The results from the treatment groups showed that the amount of TNF-α in the treatment group has decreased compared with the positive control group and it is consistent with the research conducted by Yuliawati (2012) about a decrease in TNF-α levels after administration of *Pediococcus pentosaceus* bacteria in inflammatory diarrhoea rats. This is due to Lactic Acid Bacteria found in *dadih* produces lactic acid which can hamper the growth of harmful bacteria. Furthermore, nisin as a byproduct is natural antibiotic beneficial to neutralize pathogenic bacteria. This indicates that *dadih* may also be classified as probiotic food product due to the fact that it originates from fermented milk and contain lactic acid (Purwanti *et al.* 2011).

Research on *Pediococcus pentosaceus* has not been popular and there are only few of them. It makes researches on probiotic that have been done in the past becoming a reference for the research on *Pediococcus pentosaceus* as all the probiotic bacteria have the same function and benefit. Decreased levels of TNF-α after administration of probiotic bacteria has a mechanism of action which

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is not known with certainty, but there are several mechanisms that seem to involve in the treatment of periodontal disease (Bonifait *et al.* 2009):

1. Probiotic bacteria secrete two types of bacteriocins, two of them are reuterin and reutericyclin which can inhibit the growth of pathogenic bacteria; Research conducted by Stamatova *et al.* (2007) and Koll-Klais *et al.* (2005) in Barlow (2010) mentioned that Lactobacillus rhamnosus, Lactobacillus bulgaricu and Lactobacilli strains were able to inhibit the growth of *Porphyromonas gingivalis* up to 82% and is able to inhibit the pathogenic effects produced by those bacteria.
2. Probiotic bacteria have the ability to compete with the pathogen bacteria.
3. Probiotic bacteria have anti-inflammatory effects that can inhibit the secretion of pro-inflammatory cytokines. These three mechanisms have the directly and indirectly effect to cure periodontal disease

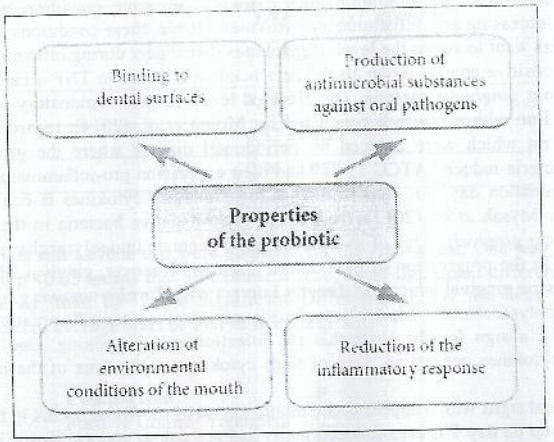

Figure 3 : Ideal properties of a probiotic intended for use in disorders of the mouth (Bonifait *et al.* 2009)

Effects of probiotics in decreasing the secretion of proinflammatory cytokines are associated with the decreased activity of Nuclear factor kB (NFkB) (the exact mechanism is still unknown). This is consistent with a research conducted by Kusuma *et al.* 2008 regarding the effects of supplementation of Lactobacillus strain LIS10506 or LIS20506 that can inhibit the activity of NFkB and significantly inhibited the expression of TNFR 1 (which has a value equal to the TNF-α).

Research that supports this study is a research conducted by Shadnoush *et al.* 2013 about the effect of Lactobacillus paracasei B 20160 on the level of pro and anti-inflammatory cytokines. The results of multidimensional showed correlation between NFkB and pro-inflammatory cytokines. When the pro-inflammatory cytokines increase, it may also increase the activity of NFkB, and the NFkB brings positive effect on the expression of cytokines such as TNF-α which can aggravate inflammation. NFkB is a transcription factor that plays important role in inflammatory condition especially the secretion of inflammatory cytokines.

Other research that supports this study about *lactobacillus* strain showed that probiotic can reduce gingiva inflammation and the number of black-pigmented bacteria such as *Porphyromonas gingivalis* which is saliva and subgingival plaque. The use of bacteria which has benefit as Lactic Acid Bacteria (LAB) supported with scaling and root planning (SRP) can block phatogenic bacteria growth in periodontal pocket and reducing probing bleeding in animal trial. The other clinical trial showed improvement in moderate to severe gingiva inflammation and probing of adult patient after

using probiotic tablet regularly. Another research proved that consuming probiotic gum in two weeks can decrease proinflammatory cytokine in gingivitis patient (Vivekananda *et al.* 2010).

The other research was done by Riccia *et al.* (2007) in Bonifait *et al.* (2009) about anti inflammation effect of *Lactobacillus brevis* in chronic periodontitis patient. This study used inhalation method, the patient inhaled refreshing concentrate for throat that contain *Lactobacillus brevis* for four days. After four days there was improvement in disease severity based on clinical parameters that can be seen: plaque index, gingival index and bleeding in probing of all patients. In addition to the indexes, there was also decreasing of prostaglandin E2 (PGE2) and matrix metalloproteinases (MMPs) of patient saliva. In this case Riccia *et al* concluded that *Lactobacillus brevis* had ability to block nitrite oxide so that the activity of PGE2 and MMPs which are inducted by nitrite oxide can be reduced. Utilization of probiotic in periodontal disease very related to immune activity that is produced by probiotic bacteria (Joseph, 2014). In vitro study by Nara *et al* showed that *Lactobacillus sp* stimulated osteoblast cell formation. The osteoblast cell formation is very important in improving bone damage that is caused by periodontal disease (Chatterjee *et al.* 2010).

Based on the research author have suggestions :

1. Changing the design of research into pre and post is necessary because each mouse has different stress resistance, hence the increase in the levels of TNF-α can be definitely caused by the treatment given by the researchers.
2. The next study should provide training to rat blood sampling conditions particularly for the negative control group because that group were never given any treatment.
3. Research on the improvement of other pro-inflammatory cytokines such as interleukin should be more specific.
4. The next studies should compare the levels of TNF-α in inflammatory periodontal tissue of rat that were given and were not given the *dadih* .
5. The next research should compare the levels of pro and anti-inflammatory cytokines which are associated with *dadih* effectiveness in the inflammatory cytokines

V. CONCLUSION

Pediococcus pentosaceus bacteria which were isolated from *dadih* can affect the levels of TNF-α in periodontal tissue inflammation induced by *Porphyromonas gingivalis* bacteria.

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TRADITIONAL VILLAGES INVOLVEMENT: A REFLECTION OF *TRI HITA KARANA* FOR TOURISM STRATEGY IN BALI

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ABSTRACT

Tourism development, in the long term, will potentially give negative impact and remove local values. In order to protect the existence of local values, Bali particularly possesses traditional villages functioned to preserve the equality of God, human, and nature as well as being reflected in *Tri Hita Karana* concept. This research aims to observe the problems in synergizing local values and tourism development in Bali. Adopting qualitative approach, there were primary and secondary data obtained through literature reviews. The result of this research shows that Bali is still lack of traditional villages involvement in creating tourism development plan. Economical rationality remains as the basic of all performed tourism development activities. Hence, *Tri Hita Karana* concept must immediately be revived by involving traditional villages in constructing sustainable tourism development strategy.

Keywords : Tourism, Traditional Villages, *Tri Hita Karana*

1. INTRODUCTION

As the main tourism destination in Indonesia, it is inevitable for Bali to deal with various tourism issues. Several literatures agree that tourism has been largely contributing to support economic growth (Andraz, Nelia, and Norte, 2015; Katircioglu, 2009; Kim, Chen, and Jang, 2006; Lee and Chang, 2008) as the catalyst to reducing poverty and providing benefits for public by upscaling productivity and employment (Stylidis and Matina, 2014; Andraz, Nelia, and Hugo, 2015; Zeinali, et.al, 2015). It is visible that the number of tourism sector contribution to raising Regional Gross Domestic Product (RGDP) of Bali which is always above 30% from the total amount. The significant number is lifted up by the tendency of the number of tourists and how they allocate their money for spending each day (BPS, 2014).

At the other hand, tourism also brings negative influence (Besculides, Martha, and Peter 2002). The open and interactive character of tourism end up with boosting cultural assimilations (Surwiyanta, 2003). Tourism, at first, gives positive impact towards economy and uplifts the level of participation of society, yet it is not guaranteed to last for any longer period. The fact is that tourism creates social externality which apparently influences society (Picture 1) (Doxey, 1976; Butler 1980; Chao, Barat, and Pasquale, 2003).

Doxey (1976) divides the effect of tourism into four stages. The first stage is **euphoria**, in which tourism is claimed to give positive contribution towards the economy. The second stage is **apathy**, indicated by the accustomed behaviour of society towards raising number of tourists. In this stage, matters of interpersonal relations start to shift into formal relations (trading partnership). Subsequently, the **annoyance** stage happens in which the domination of tourism emerges social problems such as (i) traffic jam; (ii) population density; (iii) Conflicts about land-ownership and investment; (iv) commercialization of rituals; (v) impersonal and individualist social relationship; and (vi) the negligence of local community participation in improving tourism development. Those are the