

The Role of *L. plantarum* as an Immunomodulator Secretion of Transforming Growth Factor- β 1, Transforming Growth Factor- β 3, and Interferon- α Macrophages and Dermal Fibroblasts

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ABSTRACT— *This research aims to see the effect of L.plantarum in modulating the secretion of Transforming Growth Factor-TGF β 1, TGF β 3 macrophages and fibroblasts, Interferon-IFN α macrophages, and to analyze the possibility of L.plantarum potency in supporting the process of scarless wound healing. The culture of peritoneal macrophages was treated with L.plantarum for 24 hours, while another macrophage was S.aureus stimulated for 6 hours before treatment of L.plantarum for 24 hours. The formed supernatant was separated and centrifuged to serve as a treatment on the culture of rat dermal fibroblasts for 24 hours. The supernatant was then separated and centrifuged; its cytokine level was measured with enzyme-linked immunosorbent assay-ELISA. Treatment of L.plantarum with medium and high doses increased the secretion of IFN α macrophages compared with the control; all L.plantarum doses can stimulate the secretion of TGF β 1 fibroblast and TGF β 3 macrophage significantly, but it does not affect the secretion of TGF β 1 macrophages. It can be concluded that L.plantarum increased the secretion of IFN α macrophages higher than the treatment preceded by S.aureus stimulation. The secretion of TGF β 1 fibroblasts and TGF β 3 fibroblasts also increased, but it was not as high as L.plantarum treatment stimulated by S.aureus. Therefore, the application of L.plantarum to support the process of wound healing, prophylactic of the excessive scar and fibrosis can be researched further.*

Keywords— *L.plantarum*, TGF β 1, TGF β 3, IFN α

1. INTRODUCTION

Skin is one of areas in human body inhabited by a complex ecosystem with thousands of microbe species, including *Lactobacilli*. There are many researches about benefit of probiotic and several mechanisms which allow probiotic to affect health. Host-microbe interactions underlie the mechanism of *Lactobacilli* until it has an important role in the physiology of host.

The modulation of immune response has been acknowledged as one of several benefits of probiotic. In order to modulate the immunity, the probiotic microbe must communicate with the immune cells equipped with the receptor which is able to identify the molecule from microbe-PRRs. *Lactobacilli* can cause innate and adaptive immune responses on host through the bond on pattern recognition receptors-PRRs on the surface of macrophage cells. The interaction between PRRs and microbe-associated molecular patterns-MAMPs on macrophages causes a signaling sequence[1],[2]. The signaling pathways of *Toll-like* receptors-TLRs will activate the transcription factors and stimulate the cytokine secretion and growth factors by macrophages[3],[4].

During wound healing process, *transforming growth factor-beta*-TGF β 1 and TGF β 3 play important role in inflammation, angiogenesis, re-epithelialization, and regeneration of connective tissue. TGF β 1 facilitates the recruitment of inflammation cells and improves the function of macrophage in tissue debridement[5],[6]. However, TGF β 1 also plays a role in fibrosis pathogenesis. Meanwhile, TGF β 3 plays a very important role in stopping the final differentiation in the healing process, so TGF β 3 is able to hamper the excessive scar and improve better collagen organization[7],[8]. Furthermore, *interferon alpha*-IFN α can be produced by almost all cells on the response of infection from virus and bacteria. On the macrophage cells, IFN α is produced as the result of bond of TLR3 and TLR9 with microbe DNA, and the induction of *interferon regulatory factor*-IRF7 transcription factor and expression of IFN genes type I. Due to its

apoptotic effect on fibroblasts, IFN α has been used for fibrosis therapy on several tissues, but its side effect limits the use of IFN α for therapy at last[9],[10].

Probiotic modulates the host immune response through macrophage cells[11]. Several cytokines produced by macrophages cause the in-depth effect on fibroblast migration, proliferation, production of extracellular matrix, and several cytokines and growth factors[12]. Based on several research results, *L.plantarum* can modulate the host immune response, so it is able to modulate the secretion of several cytokines and growth factors, such as TGF and IFN[13]. The production of cytokine and growth factor during the healing process depends on the regulation preceded by communication between macrophages and fibroblasts, and virulence factor from microbe[14]. Since virulence of *L.plantarum* on human skin is low[15], our hypothesis is that *L.plantarum* is able to activate the proinflammatory response, but it is not on par with the pathogen microbe. Therefore, this research is conducted to see the effect of *L.plantarum* in modulating the secretion of IFN α macrophages and TGF β 1, TGF β 3 secreted by macrophages and fibroblasts, and to analyze the possibility of application of *L.plantarum* in promoting the process of *scarless* wound healing.

2. MATERIAL AND METHODS

2.1 Animals.

For this experiment, 6-week old male *Rattus norvegicus*-Wistar rat were used. Rat received a normal diet and water *ad libitum*, and were kept in isolation at a constant temperature of 24°C and humidity, with a cycle of 12 h light/12 h darkness, in animal house of Eijkman Education Hospital. Rat were sacrificed by cervical dislocation. The tenets of the Declaration of Helsinki were observed, and institutional animal experimentation committee approval was granted.

2.2 Peritoneal macrophages-Pm culture.

Macrophage cells obtained from rats, were washed 3 times, counted, and their viability was assessed with Trypan blue. Afterward, the macrophages was cultured in RPMI 1640 + 3% fetal calf serum (FCS) in an incubator 5% CO₂ at 37°C for 45 minutes to allow macrophages attaching to the plate; then macrophages was displaced into a number of wells, 0.5 x 10⁶ cells/well. The treatment may begin 4-24 hours after plating[16].

2.3 Skin dermal fibroblast culture.

A sample of rat skin that has been minced 2-3 mm² in size was transferred into a plate that contained DMEM + 10% FCS; the fibroblast cells attached were cultured in an incubator 5% CO₂; at 37°C till achieved confluence. The third passage fibroblasts that have assessed the viability of which has been examined was then transferred in a number of wells, 0.5 x 10⁵ cells/well, and now ready to do treatment with the supernatant of macrophages culture for 24 hour. Then, the supernatant was separated for measuring cytokines levels. Medium and chemical were from Sigma-Aldrich (Life science, St. Louis, MO)[16].

2.4 Microbial cultures.

An ATCC25923-derived *S.aureus* was cultured in a Mueller Hinton (Oxoid, Thermo Scientific, UK) and incubated at 37°C for 24 hours in an aerobic condition. An ATCC8014-derived *L.plantarum* was cultured in a Mann-Rogosa Sharpe broth (Difco, Detroit, MI) and incubated at 37°C for 24 hours in an anaerobic condition. The cultures were harvested at a *mid-log* phase and then a bacterial suspension was made by comparison with McFarland standard, adjusted to an approximate concentration of 10⁶,10⁷,10⁸cfu/mL (*S.aureus*-Sa) and 10⁶,10⁷,10⁸ cfu/mL (*L.plantarum*-Lp), and confirmed by spectrophotometer. Furthermore, a killing process was done by heating in a waterbath at 70°C for 30 minutes, and then left at room temperature and stored at 4°C until its use. Medium were purchased from Oxoid (Thermo Scientific, UK).

2.5 Stimulation of macrophage cells with *S.aureus* and treatment of *L.plantarum*.

The overnight incubated peritoneal macrophages cell culture, 0.5 x 10⁵ cells/well was then stimulated by Sa at dosages of 10⁶,10⁷,10⁸ cells/mL for 6 hours. Supernatant was removed and washing was done by RPMI twice, and then Lp was added at dosages of 10⁶, 10⁷, 10⁸ cells/mL (Lp and SaLp), incubated for 24 hours before detecting macrophages cytokine levels. 100 μ L macrophages supernatant transferred to fibroblast culture, incubated for 24 hours. After that, collected supernatant was centrifuged at 2000 g for 10 minutes, then fibroblast culture supernatant was transferred into an ELISA plate for the measurement of the fibroblast cytokine levels.

2.6 Cytokine determination by ELISA.

Cytokine concentration in culture supernatants were assayed by sandwich ELISA. TGF β 1, TGF β 3 were determined using a mouse anti-rat TGF β 1-TGF β 3 mAb as the capture Ab and a biotinylated mouse anti-rat TGF β 1-TGF β 3 mAb as a detection Ab. To determine IFN α levels, mouse anti-rat IFN α mAb as the capture Ab and a biotinylated mouse anti-rat IFN α mAb as a detection Ab. The absorbance of each micro plate was read using 450 nm as the primary length and 570

nm as the reference wave length. All test were done in triplicate. All of these Abs and recombinant cytokines were purchased from Cloud-Clone Corp USA.

2.7 Statistical analysis.

The data were analysed by SPSS 21 software using one way ANOVA and Tukey's Post Hoc mean comparison test. A value of $p < 0.05$ was considered as statistically significant.

3. RESULTS AND DISCUSSION

3.1 *L.plantarum* stimulates the production of TGFβ1 fibroblasts, but not with TGFβ1 macrophages.

After 24 hours of *L.plantarum* treatment on fibroblast culture, the production of TGFβ1 cytokines increased significantly ($p < 0.05$), while the increase of TGFβ1 macrophages only happened on *L.plantarum* treatment with high dose compared with the increase of TGFβ1 caused by *S.aureus* treatment with the lowest dose (Figure 1.a-b). *L.plantarum* treatment preceded by stimulation of *S.aureus*-SaLp also caused the increase of fibroblast TGFβ1 level, but it did not happen on macrophages culture.

3.2 The highest level of TGFβ3 macrophages was caused by Lp treatment with 10^6 dose; while the highest TGFβ3 fibroblasts level was caused by Lp treatment with 10^8 dose.

Lp treatment with low dose on macrophages culture increased TGFβ3 level, along with the increasing Lp dose, TGFβ3 macrophages kept decreasing, but SaLp produced higher level of TGFβ3. As shown in Figure 1.c-d, the highest TGFβ3 content was achieved with SaLp treatment of high dose on macrophages culture as well as fibroblasts. It seems that high level of TGFβ3 macrophages correlated with the increase of TGFβ3 on fibroblast culture.

3.3 The highest level of IFNα macrophages was achieved with 10^7 dose Lp treatment.

Figure 1.e shows that Lp treatment on macrophages culture successfully stimulated the production of IFNα, but it was not as high as the level achieved by Lp; Sa stimulation on SaLp treatment also successfully improved IFNα level significantly ($p < 0.05$). It seems that IFNα resulted from the stimulation of *S.aureus* with the lowest dose for 6 hours caused high IFNα level. Along with the increase of stimulation dose, IFNα level also increased too. (data are not shown).

3.4 Correlation between TGFβ1 macrophages and TGFβ3 fibroblasts.

Figure 2.a-c. Sa stimulation preceding the Lp treatment on macrophages culture-SaLp, such as Lp treatment, correlated with the increase of TGFβ1 and TGFβ3 level on fibroblasts culture ($p < 0.01$).

Many researchers have understood that the surface microflora affects the innate and adaptive immune system. The beneficial effect of microflora in the gastrointestinal tract supports the use of probiotic[17]. Probiotic in the process of wound healing has been used by the researchers with the promising result[18],[19]. Our research aims to analyze the role of *L.plantarum* on the secretion of some cytokines resulted from the culture of macrophages and fibroblasts *in vitro*. TGFβ1 is one of cytokines which can function as the pro-inflammatory cytokines and the anti-inflammation at other times[7],[20]. The inflammation phase on wound healing process is dominated by inflammation cells, such as macrophages through cytokines and the resulting growth factor[21]. In this research, macrophages culture is challenged with several treatments involving *S.aureus* as the stimulant and *L.plantarum* in which cytokine level of supernatant is then measured with ELISA.

Peritoneal macrophages-Pm is the most mature type of cell compared with bone marrow-Bm and spleen-SPm macrophages [22]; it is the reason of researcher to use MP as one of research objects. Besides, macrophages is a cell which can transform from macrophage pro-inflammatory phenotype to alternative/reparative phenotype; this transition is a requirement for change from inflammation phase to proliferation phase on wound healing process[20],[21]. The production of cytokines and growth factors during the healing process depends on the regulation preceded by crosstalk between several cells on the injured area; in this research, it is crosstalk between macrophage and fibroblast[23]. We used fibroblast cell since this cell is very important in proliferation and remodeling phases. The failure in the inflammation phase will be highly influential on the next phases and it can cause abnormality in wound healing. Besides the crosstalk between macrophage and fibroblast, the cytokines level is also affected by the factor of microbe virulence. The difference between *Lipoteichoic acid*-LTA *L.plantarum* and LTA pathogen, such as *S.aureus*, depends on the amount of third acyl chain and the degree of acyl chain saturation, and the sugar substitute on Gro-P chain (glucose and galactose on *L.plantarum*, GlcNAc on *S.aureus*), [15],[24] which makes *L.plantarum* an activator of TLR2 and low inducer of TNFα for macrophages. When a microbe is more virulent, the induction of cytokine production is higher, and vice versa[14]. Thus, based on our result, the highest level of IFNα macrophages as the consequence of challenge with high-dose Lp, was as not as high as IFNα level due to the challenge with *S.aureus* (the data are not shown).

Besides *T lymphocyte regulator*-Treg cells, finding of our research, macrophages also secreted TGFβ1. Although it is not too significant, the increase of TGFβ1 macrophages as the result of Lp treatment in this research shows that this species is able to modulate the function of macrophages in secreting growth factor which is very important in wound healing. The optimal TGFβ1 level is highly required in regulating the function of another cell in this process, such as fibroblasts. At the right time, fibroblast needs to be activated through cytokines and growth factors secreted by

macrophages. TGF β 1 is very important in fibroblast activation to proliferate and differentiate and to produce TGF β fibroblast which can stimulate and reduce the required function of fibroblast[21],[23].

Our research shows the increase of TGF β 1 and TGF β 3 fibroblast level after challenged with supernatant containing macrophage TGF β 1. It shows that macrophage TGF β 1 can stimulate the production of TGF β 1 and TGF β 3 by fibroblast, as seen at fig. 2, which means that macrophages definitely controls fibroblast function in producing growth factors which is very important in wound healing process. It also applies to stimulation of *S.aureus* preceding Lp treatment.

It has been known that there are 5 types of TGF β ; three of them (TGF β 1, TGF β 2, and TGF β 3) are in mammals, including human being. The balance between TGF β 1 and TGF β 3 is the important regulator in forming the scar[6],[7]. High TGF β 1 level on maturation and remodelling phases will affect the excessive forming of scar; on the contrary, high TGF β 3 level in this phase will reduce the forming of scar and keloid. Some researchers have successfully reduced the forming of scar with recombinant TGF β 3 as new prophylactic therapy[8]. It seems that TGF β 1 and TGF β 3 resulted from macrophages in our laboratory is successful in improving TGF β 3 production by fibroblast; Lp with high dose induces TGF β 3 level. It requires *in vivo* research to prove that Lp can reduce the excessive scar as the consequence of high TGF β 3 level.

Another interesting finding is that the lowest fibroblast TGF β 1 level was caused by Lp treatment stimulated with *S. aureus*, while SaLp with high dose induces the highest TGF β 3 level. It seems that this combination needs to be proved with *in vivo study* to determine whether or not the stimulation of *S.aureus* is highly influential in prophylactic for forming excessive scar.

As one of *antigen presenting cells-APC*, macrophages is completed with several molecule-identifying receptors which are antigens known as TLRs, with the capability to identify MAMPs from *L.plantarum*. *D-alanin* in LTA from *L.plantarum* can bind to TLR2, TLR4, while its genetic material binds to TLR3 or TLR9 and then triggers the signaling cascade which ends with the production and secretion of IFN[2],[11],[15].

Besides the result of virus infection, *cytosine phosphate guanosine-CpG-A* from bacterial DNA can also stimulate production of IFN type I (IFN α and IFN β)[2], and its effect exceeds fighting the infection. It is known that IFN α and IFN β can reduce the fibrosis occurrence on several tissues. Clinically, these two interferons have been used with several success rates on the cases of keloid and burns[9]. Interferon can regulate the expression of genes related to apoptosis of fibroblast cell and sensitize several types of cell on the apoptosis stimuli, but the side effect limits the use of this therapy at last for prophylactic of scar and keloid[25],[26].

Unmethylated CpG-DNA bacterial actually has different capability, between pathogen and commensal in stimulating TLR9, in which this capability correlates with the existence of *unmethylation CpG*[27]. It seems that in commensal bacterium, including Lactobacilli, suppressive motif (*poly guanosine*) is found more frequently with the capability to prevent the activation of *dendritic cells-DC* and maintain *Treg* conversion[28]. Therefore, the researcher assumes that the increasing production and secretion of IFN as the result of *L.plantarum* treatment in our research is not as high as the IFN level caused by pathogen-*S.aureus* treatment (data are not shown) based on the result we got. It seems that the capacity of regulator from CpG motif in the research of Bouladoux, *et al* also applies to the macrophages cell treated by *L.plantarum* due to its CpG motif. It can also explain how macrophage can produce and secrete TGF β 1-TGF β 3, which are usually produced by *Treg*.

Based on our result, *L.plantarum* is proven to induce the secretion of IFN α twice than the control ($p < 0.05$), and the stimulation of *S.aureus* preceding Lp treatment as well, but it is lower. It supports previous research that macrophages is one of immune cells which is able to secrete IFN α after challenged by microbe treatment. However, the increase of IFN α level is not as high as what is resulted by macrophages as the result of *S.aureus* treatment with high dose (data are not shown). It happens since LTA molecule from *Lactobacillus* is weak immune-stimulatory trait[15]. Interestingly, although it can be useful, an extremely high IFN α level probably causes the unwanted side effect, such as recombinant IFN therapy. IFN α level which is not too high due to the *L.plantarum* treatment seems to be beneficial.

The proof that *L.plantarum* causes wound healing acceleration by some previous researchers is supported by the result in which *L.plantarum* treatment can increase the deposit of extracellular matrix, macrophages infiltration, the forming of granulation tissue, and epithelization acceleration[19],[29], proven with the increasing levels of TGF β 1, TGF β 3, and macrophage IFN α in our research.

4. CONCLUSION

In the last few years, our understanding on probiotic mechanism in curing several inflammation diseases have grown rapidly, and the role of *L.plantarum* in modulating secretion of several cytokines and growth factors has been known. Based on the result of our study, it can be concluded that *L.plantarum* plays a role in modulating secretion of TGF β 1 macrophages and fibroblasts, TGF β 3 macrophages and fibroblasts, and macrophages IFN α . Therefore, the application of *L.plantarum* to support the process of wound healing, prophylactic of excessive scar, and fibrosis can be researched further.

5. ACKNOWLEDGMENT

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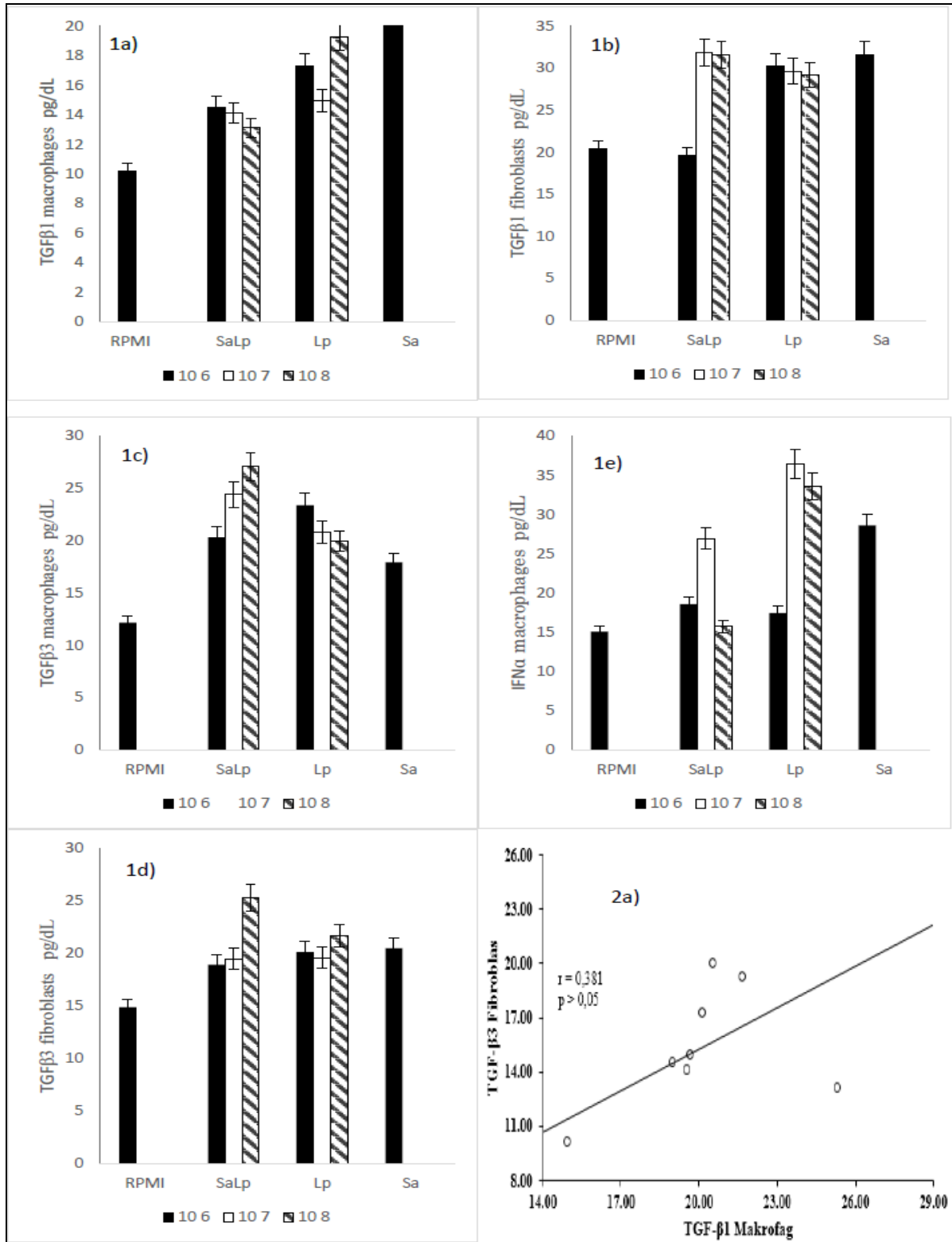


Figure 1. Effects of SaLp and Lp treatment on macrophage cells and fibroblasts culture of different cytokines in rats. The cytokine levels determined by Elisa for TGFβ1-(1a-1b), TGFβ3-(1c-1d), and IFNα-(1e) from RPMI as control, *L.plantarum*-Lp, *S.aureus*-*L.plantarum*-SaLp, and *S.aureus*-Sa. Data shown are the means ± SD of 3 animals. P values for all significant comparison ($p < 0.05$) are represented.

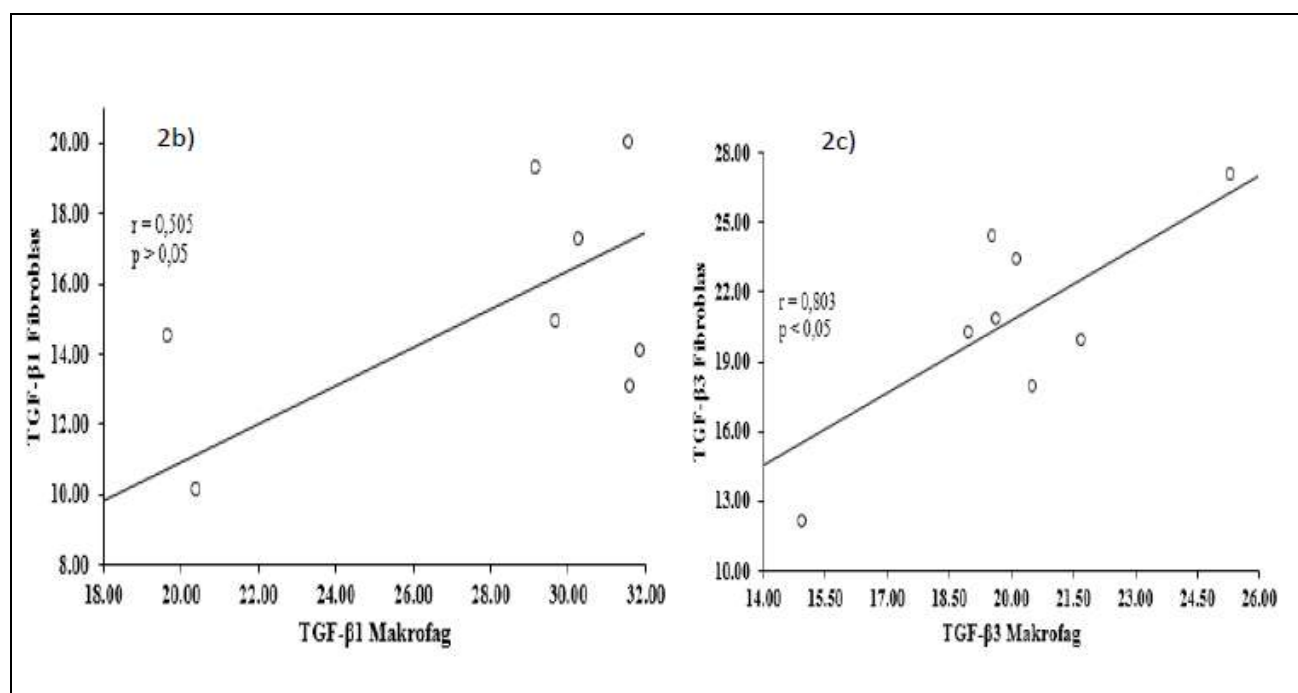


Figure 2. The relationships between TGFβ1 macrophages-TGFβ3 fibroblasts (2a), TGFβ1 macrophages TGFβ1 fibroblasts (2b), and TGFβ3 macrophages TGFβ3 fibroblasts (2c), were determined by the Pearson correlation analysis. Data are presented as means ± SD and significance is denoted as $p < 0.05$

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