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Research Report

Acceleration of fibroblast number and FGF-2 expression using *Channa striata* extract induction during wound healing process: in vivo studies in wistar rats

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ABSTRACT

Background: *Wound healing is a biological process associated with tissue growth and regeneration. Wound healing process, is important to repair damaged tissue. Wound healing process consists of coagulation and hemostasis, inflammation, proliferation, as well as remodeling phases. The process can be accelerated by taking synthetic or non synthetic drugs. One of them is Channa striata extract. The extract contains albumin, copper, and zinc, which can be assumed to increase inflammatory cell infiltration, fibroblast proliferation, and collagen secretion.* ***Purpose:*** *This study aimed to reveal the effects of Channa striata extracts on fibroblast number and FGF-2 expression in mucosal wound healing process of the Wistar rats' lower lip.* ***Method:*** *This research was a true laboratory experimental research with randomized post test only control group design. Samples of experiment were devided to experiment and control group that consist five samples each. Experimental group was treted with Channa striata extract and ethanol at concentration of 25%, 50%, and 100%. The fibroblast number and FGF-2 expresion were examined.* ***Result:*** *The number of fibroblasts in the treatment groups receiving Channa striata extract at concentrations of 25%, 50%, and 100% was higher than in the control group. The highest number of fibroblasts was found on day 3 at the concentration of 100% ($p<0.05$). Similarly, FGF-2 expression in the treatment groups receiving Channa striata at concentrations of 25%, 50%, and 100% was higher than in the control group. The highest expression of FGF-2 was found on day 3 at the concentration of 50% ($p<0.05$).* ***Conclusion:*** *Channa striata extract increased fibroblast number and FGF-2 expression in mucosa wound healing process.*

Keywords: *Channa striata extract; FGF-2; fibroblast; wound healing*

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INTRODUCTION

Oral cavity is an integral part of the body often traumatized when performing its functions. Trauma can occur intentionally or unintentionally causing wounds to the oral mucosa omitted.[1,2] Wounds constitute a change of continuity in anatomical and cellular tissues that can occur on skin or mucosa. Damage to the continuity, can be improved through wound healing process.[3]

Wound healing process is a complex cellular and vascular process. The process aims to restore the integrity of the structure and function of damaged tissue. Wound healing process generally consists of four phases, namely coagulation and homeostasis, inflammation, proliferation, and remodeling. Histologically, the results of wound healing process can be indicated by density of collagen fibers produced by fibroblasts in new connective tissue in the phase of proliferation.[4] Fibroblasts first appears on day 2-3 after the injury in conjunction with the formation of new capillaries which will provide sufficient supply of nutrients for cell proliferation. The proliferation of fibroblasts and the formation of new capillaries are triggered by growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2).

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FGF-2 is one of the growth factors secreted by macrophages. FGF-2 expression increases immediately after the injury, and reaches its peak on days 5-8. Fibroblasts regulate angiogenesis via secretion of these growth factors. In addition, fibroblasts also produce collagen type I, III, V and other extracellular matrix components.[5,8,9] In the final phase of wound healing process or remodeling process, the expression of collagen type III drops and is replaced with increased expression of collagen type I.[10] Fibroblasts then migrate into the wound tissue and reach the maximum number on days 7-14 after the injury. [11] In experimental researches on traumatic ulcers on the buccal mucosa of Wistar rats show that on day 7 after injuries, the ulcers will experience cicatrix, the color of mucosa will be normal, and the edge of ulcers will disappear.[12]

Wound healing process actually can be accelerated by using certain agents, one of which is *Channa striata* extract. *Channa striata* extract plays an important role in wound healing process.[13,14] This is because *Channa striata* extract contains high albumin. Albumin is indispensable in human body every day, especially in the process of wound healing. Other researches also have reported that *Channa striata* extract also contains compounds essential for the human body, including zinc (Zn), copper (Cu), and iron (Fe), which play a role in enhancing immunity. In addition, Cu is reported to increase VEGF, so angiogenesis increases.[13-15] In other researches, copper is reported to increase FGF-2 that plays a role in the proliferation of fibroblasts and the expression of collagen type 1, so tissue structure in the wound healing process can be repaired faster.[16,17]

Channa striata extract is one of the traditional medicines with huge potential. In the last decade, traditional medicine is increasingly popular. Traditional medicinal products can be made from animals or plants, widely used as an alternative treatment to meet the basic needs of people in the health field. The advantages of using traditional medicine are cheap, easy to obtain, and minimal side effects compared to chemical drugs.[14] Indonesia, especially Kalimantan, is a natural habitat for *Channa striata*. In addition to its distinctive taste, eating *Channa striata* for South Kalimantan people can accelerate wound healing process.

For those reasons, this research aimed to determine the effects of *Channa striata* extract on the mucosal wound healing process of Wistar rats' lower lip histopathologically and immunohistochemically on days 3, 5, and 7. In other words, this research focused on analyzing acceleration of fibroblasts count and FGF-2 expression in the mucosal wound healing process of Wistar rats' lower lip.

MATERIALS AND METHOD

This research was a true laboratory experimental research (true experimental design). This research used randomized design post test only control group design. In this research, the number of samples to be examined was calculated using Lemmeshow's formula. The total samples of each group was five samples.

The research materials and instruments used in this research were *Channa striata* samples, aquadest, 50% ethanol, buffer formalin, cotton buds, ether, xylol, paraffin, reagents FGF-2, hematoxylin eosin staining, becker glass, stirer, pipette, oven, scales, mixer glass, vibrator, test tube racks, thermometers, autoclave, measuring cup, tweezers dentistry, glass mouth, burnisher, burner, disposible syringe 2.5 ml, excavators, sample bottle, label, slide and cover glass, petri disks, lights, gloves, and cover mouth. Independent variables of this research were *Channa striata* extract and ethanol at a concentrations of 25%, 50%, and 100% as well as aquadest as a control group.

Before conducting an examination on experimental animals, this research design was submitted to the Health Research Ethics Commission in Faculty of Dental Medicine, Universitas Airlangga in order to be approved. Animals in the control and treatment groups were anesthetized in order to make them feel painless at the beginning of treatment. Those animals were put into glass tubes essentially given a cloth that had been soaked in a solution of 10% ether, and then sealed. They were waited to fall asleep.

The mucosa of their lower lip then got asepsis with 0.12% clorhexidine digluconate. The mucosa of their lower lip was injured with a scalpel heated for 1 minute and touched for 1 second. The size of the wound was 10 mm with a depth of 1 mm. After the rats free of anesthetic, they were kept in a cage and fed in moderation. Treatment given can be seen in Table 1. The fibroblast number and FGF-2 expression were examined,

RESULTS

Based on the results of observation and measurement with fibroblast parameters, there were four groups, namely control group, treatment group with a concentration of 25%, treatment group with a concentration of 50%, and treatment group with a concentration of 100%. The mean number of fibroblasts at each concentration of the extract on days 3, 5, and 7 can be seen in Table 2.

Table 2 shows that the mean number of fibroblasts in the treatment groups was higher than in the control groups. The highest number was found in the treatment group receiving *Channa striata* extract at the concentration of 100% on day 3, but decreased from day 5 to 7. However, the mean number of fibroblasts in the treatment group receiving *Channa striata* extract at the concentration of 100% was generally higher on days 3, 5 and 7 than the other treatment groups at the other concentrations. The results seen in Table 2 were also confirmed by microscopic histopathological examination on fibroblasts in each research group on days 3, 5, and 7 as depicted in the following Figure 1.

Figure 1 shows that based on the results of the histopathological examination, the number of fibroblasts on day 3 in the treatment groups receiving *Channa striata*

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Table 1. Classifying and treatment of the experimental animals

Group	Types of treatment	Doses	Decapitation
1	Aquadest	2.5 ml/ day	Day-3
2	Aquadest	2.5 ml/ day	Day-5
3	Aquadest	2.5 ml/ day	Day-7
4	25% *Channa striata* extract	10 ml/kgBM/ day	Day-3
5	25% *Channa striata* extract	10 ml/kgBM/ day	Day-5
6	25% *Channa striata* extract	10 ml/kgBM/ day	Day-7
7	50% *Channa striata* extract	10 ml/kgBM/ day	Day-3
8	50% *Channa striata* extract	10 ml/kgBM/ day	Day-5
9	50% *Channa striata* extract	10 ml/kgBM/ day	Day-7
10	100% *Channa striata* extract	10 ml/kgBM/ day	Day-3
11	100% *Channa striata* extract	10 ml/kgBM/ day	Day-5
12	100% *Channa striata* extract	10 ml/kgBM/day	Day-7

Table 2. The mean and standard deviation of fibroblasts at each concentration of the extract on days 3, 5, and 7

Day	Concentration of the extract	Mean	Standard deviation
3	Control	3.4000	1.14018
	25%	4.2000	1.30384
	50%	4.8000	.83666
	100%	5.6000	.89443
5	Control	2.6000	.89443
	25%	3.4000	.54772
	50%	4.0000	.00000
	100%	5.4000	.54772
7	Control	2.0000	1.00000
	25%	3.0000	1.00000
	50%	3.8000	.83666
	100%	4.8000	.83666

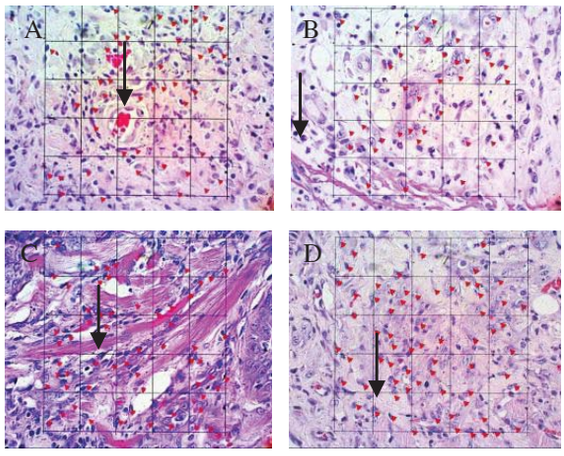

Figure 1. The results of histopathological examination on fibroblasts on day 3 in the control group (A); the treatment groups receiving *Channa striata* extract the concentration of 25% (B); 50% (C); and 100% (D).

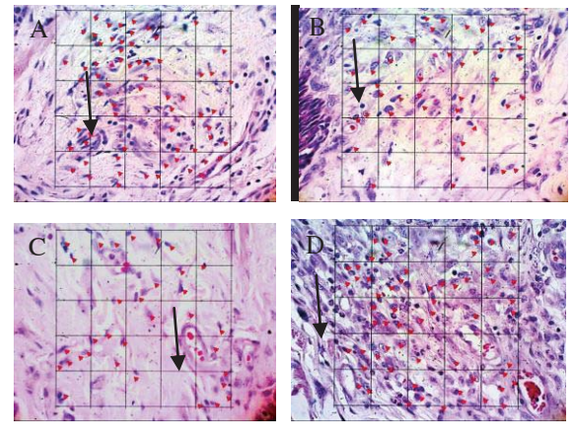

Figure 2. The results of histopathological examination on fibroblasts on day 5 in the control group (A); the treatment groups receiving *Channa striata* extract the concentration of 25% (B); 50% (C); and 100% (D).

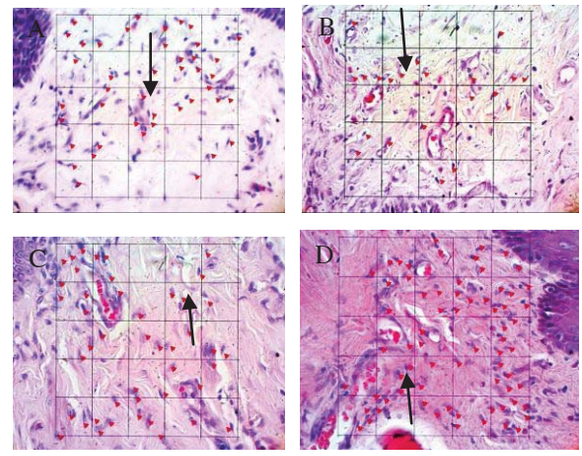

Figure 3. The results of histopathological examination on fibroblasts on day 7 in the control group (A); the treatment groups receiving *Channa striata* extract the concentration of 25% (B); 50% (C); and 100% (D).

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Table 3. The mean and standard deviation of FGF-2 expressions at each concentration of the extract on days 3, 5, and 7

Day	Concentration of the extract	Mean	Standard deviation
3	Control	8.6000	1.67332
	25%	14.6000	1.67332
	50%	18.0000	3.39116
	100%	17.8000	1.30384
5	Control	6.6000	2.07364
	25%	10.0000	3.08221
	50%	12.0000	1.58114
	100%	12.8000	1.92354
7	Control	3.6000	1.14018
	25%	7.8000	2.04939
	50%	10.0000	1.87083
	100%	13.4000	3.13050

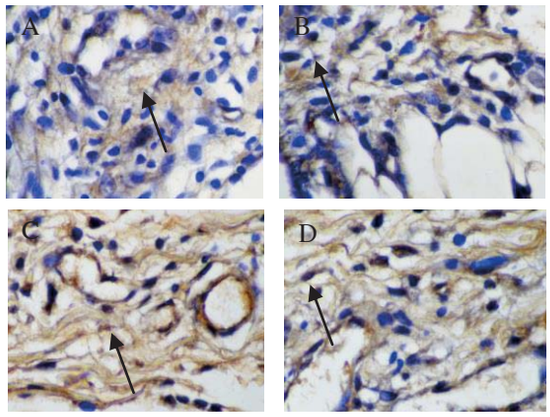

Figure 4. The results of histopathological examination on FGF-2 expressions on day 3 in the control group (A); the treatment groups receiving *Channa striata* extract the concentration of 25% (B); 50% (C); and 100% (D).

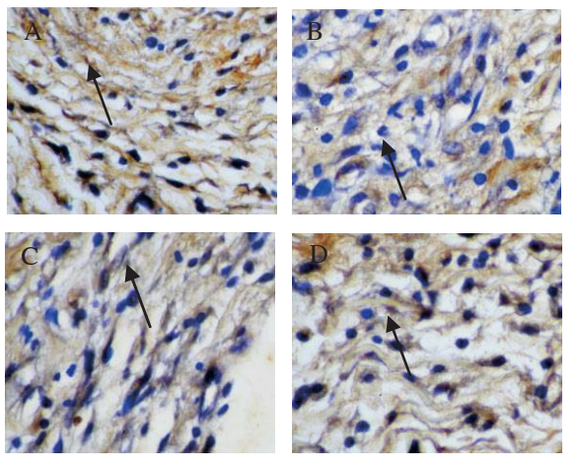

Figure 5. The results of histopathological examination on FGF-2 expressions on day 5 in the control group (A); the treatment groups receiving *Channa striata* extract the concentration of 25% (B); 50% (C); and 100% (D).

extract at the concentrations of 25% (B), 50% (C), and 100% (D) was higher than in the control group (A). The highest number of fibroblasts was found in the treatment group receiving *Channa striata* extract at the concentration of 100% (D). Furthermore, the number of fibroblasts on day 5 and 7 can be seen in Figures 2 and 3.

Figure 2 shows that based on the results of the histopathological examination, the number of fibroblasts on day 5 in the treatment groups receiving *Channa striata* extract at the concentrations of 25% (B), 50% (C), and 100% (D) was higher than in the control group (A). The highest number of fibroblasts was found in the treatment group receiving *Channa striata* extract at the concentration of 100% (D). Based on Figure 1, the number of fibroblasts on day 5 reduced compared to the number of fibroblasts on day 3.

Figure 3 shows that based on the results of the histopathological examination, the number of fibroblasts on day 7 in the treatment groups receiving *Channa striata* extract at the concentrations of 25% (B), 50% (C), and 100% (D) was higher than in the control group (A). The highest number of fibroblasts was found in the treatment group receiving *Channa striata* extract at the concentration of 100% (D). Based on Figures 1 and 2, the number of fibroblasts on day 7 reduced compared to on day 3 and day 5 (in case of measurement).

Observation and measurement of on FGF-2 expression were conducted through immunohistochemistry examination. The samples were divided into four groups, namely the control group, the treatment group with the concentration of 25%, the treatment group with the concentration of 50%, and the treatment group with the concentration of 100%. The mean expression of FGF-2 at each concentration on days 3, 5, and 7 can be seen in Table 2.

Table 3 shows than the mean expression of FGF-2 in the treatment groups was higher than in the control

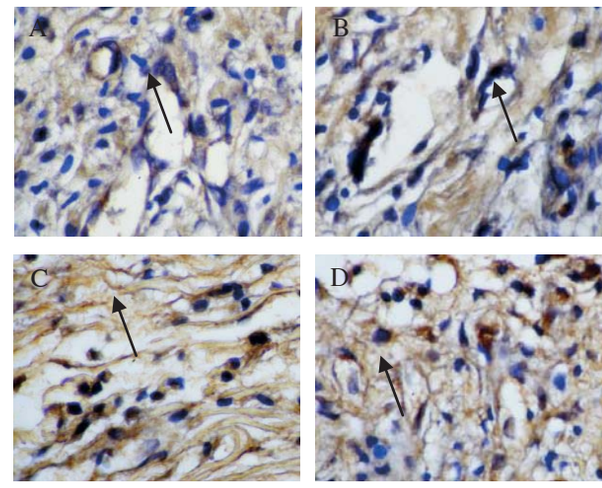

Figure 6. The results of histopathological examination on FGF-2 expressions on day 7 in the control group (A); the treatment groups receiving *Channa striata* extract the concentration of 25% (B); 50% (C); and 100% (D).

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group. The highest expression of FGF-2 was found in the treatment groups on day 3. The mean expression of FGF-2 in the treatment groups decreased from day 5 to day 7, and the highest ones at the concentration of 100%, except in the treatment groups on day 3, the highest one at the concentration of 50%.

The results as shown in Table 3 were supported by the results of microscopic histopathological examination on FGF-2 expressions in each group on days 3, 5, and 7 as seen in the following Figure 4. Figure 4 shows that the results of histopathological examination on FGF-2 expression on day 3 in the treatment groups receiving *Channa striata* extract at the concentrations of 25% (B), 50% (C), and 100% (D) were higher than in the control group (A). The highest expression of FGF-2 was found in the treatment group receiving *Channa striata* extract at the concentration of 50% (D).

The number of fibroblasts on days 5 and 7 can be seen in the following Figures 5 and 6. Figure 5 shows that the results of histopathological examination on FGF-2 expression on day 5 in the treatment groups receiving *Channa striata* extract at the concentrations of 25% (B), 50% (C), and 100% (D) were higher than in the control group (A). The highest number of fibroblast was found in the treatment group receiving *Channa striata* extract at the concentration of 100% (D). Based on Figure 4, FGF-2 expression on day 5 reduced compared to on day 3.

Figure 6 shows that the results of histopathological examination on FGF-2 expression on day 7 in the treatment groups receiving *Channa striata* extract at the concentrations of 25% (B), 50% (C), and 100% (D) were higher than in the control group (A). The highest expression of FGF-2 was found in the treatment group receiving *Channa striata* extract at the concentration of 100% (D). Based on Figures 4, 5 and 6, FGF-2 expression on day 7 reduced from day 3 to day 5.

Tables 4 show that the mean values of the three parameters in the treatment groups were higher than in the control group. The mean values in the treatment groups were higher as the concentration of the extract increased. The differences in the mean values between the treatment groups and the control group can be seen in the diagram below.

Figure 7 shows that the mean values of the three parameters in the three treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100%

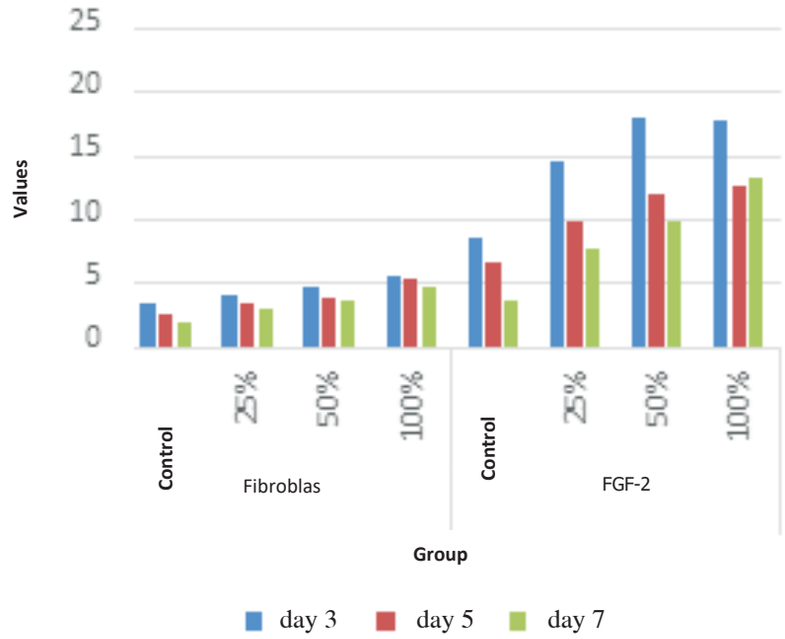

Figure 7. The mean values of the three parameters in the control group and the treatment groups.

Table 4. The significance values of difference in fibroblasts between the control group and the treatment groups on day 3

Day	Parameter	Group	Control	25%	50%	100%
Day 3	Fibroblasts	Control	-	0.250	0.053*	0.005*
		25%		-	0.384	0.053*
		50%			-	0.886
		100%				-

* There were significant differences

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Table 5. The significance values of difference in FGF2 expressions between the control group and the treatment groups on day 3

Day	Parameter	Group	Control	25%	50%	100%
Day 3	FGF-2	Control	-	0.133	0.012*	0.000*
		25%		-	0.224	0.002*
		50%			-	0.022*
		100%				-

* There were significant differences

Table 6. The significance values of difference in fibroblasts between the control group and the treatment groups on day 5

Day	Parameter	Group	Control	25%	50%	100%
Day 5	Fibroblasts	Control	-	0.126*	0.025*	0.000*
		25%		-	0.070*	0.000*
		50%			-	0.005*
		100%				-

* There were significant differences

Table 7. The significance values of difference in FGF-2 expressions between the control group and the treatment groups on day 5

Day	Parameter	Group	Control	25%	50%	100%
Day 5	FGF-2	Control	-	0.029*	0.002*	0.000*
		25%		-	0.176	0.650
		50%			-	0.579
		100%				-

* There were significant differences

were higher than in the control group. The highest mean value in almost all parameters was found in the treatment group receiving *Channa striata* extract at the concentration of 100%.

Data analysis was continued with statistical tests to analyze the significance difference in the parameters of collagen, fibroblasts, and FGF-2 among each group research. The results of the tests showed significance values among the research groups.

There were significant differences in fibroblasts on day 3 ($p<0.05$) between the control group and the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100%, between the treatment group receiving *Channa striata* extract at the concentration of 25% and the treatment groups with the concentrations of 50% and 100%, as well as between the treatment group receiving *Channa striata* extract at the concentration of 50% and the treatment group with the concentration of 100%.

There were significant differences in FGF-2 expressions on day 3 ($p<0.05$) between the control group and the treatment groups receiving *Channa striata* extract at the concentrations of 50%, and 100%, between the treatment group receiving *Channa striata* extract at the concentration of 25% and the treatment group with the concentration of 100%, as well as between the treatment group receiving *Channa striata* extract at the concentration of 50% and the treatment group with the concentration of 100%. Nevertheless, there was no significant difference between the control group and the treatment group receiving *Channa striata* extract at the concentration of 25% as well as between the treatment group receiving *Channa striata* extract at the concentration of 25% and the treatment group with the concentration of 50% (Table 5).

There were significant differences in fibroblasts on day 5 ($p<0.05$) between the control group and the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100%, between the treatment group receiving *Channa striata* extract at the concentration of 25% and the treatment groups with the concentrations of 50% and 100%, as well as between the treatment group receiving *Channa striata* extract at the concentration of 50% and the treatment group with the concentration of 100% (Table 6).

There were significant differences in FGF-2 expressions on day 5 ($p<0.05$) between the control group and the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100%, between the treatment group receiving *Channa striata* extract at the concentration of 25% and the treatment group with the concentration of 50%, as well as between the treatment group receiving *Channa striata* extract at the concentration

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Table 8. The significance values of difference in fibroblasts between the control group and the treatment groups on day 7

Day	Parameter	Group	Control	25%	50%	100%
Day 7	Fibroblasts	Control	-	0.106*	0.007*	0.000*
		25%		-	0.189*	0.007*
		50%			-	0.106
		100%				-

* There were significant differences

Table 9. The significance values of difference in FGF-2 expressions between the control group and the treatment groups on day 7

Day	Parameter	Group	Control	25%	50%	100%
Day 7	FGF-2	Control	-	0.007	0.000*	0.000*
		25%		-	0.128*	0.001*
		50%			-	0.025*
		100%				-

* There were significant differences

of 50% and the treatment group with the concentration of 100% (Table 7).

There were significant differences in fibroblasts on day 7 ($p<0.05$) between the control group and the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100%, as well as between the treatment group receiving *Channa striata* extract at the concentration of 25% and the treatment groups with the concentrations of 50% and 100%. However, there was no significant difference between the treatment group receiving *Channa striata* extract at the concentration of 50% and the treatment group with the concentration of 100% (Table 8).

There were significant differences in FGF-2 expressions on day 7 ($p<0.05$) between the control group and the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100%, between the treatment group receiving *Channa striata* extract at the concentration of 25% and the treatment groups with the concentrations of 50% and 100%, as well as between the treatment group receiving *Channa striata* extract at the concentration of 50% and the treatment group with the concentration of 100% (Table 9).

DISCUSSION

Wound healing process is a complex cellular and vascular process consisted of four phases, coagulation and hemostasis, inflammation, proliferation, and remodeling. The process can be accelerated using synthetic or non-synthetic ingredients, one of which is *Channa striata* extract.

In this study, observation on FGF-2 expression and fibroblast number was focused in wound healing process of Wistar rats' oral mucosa given and not given *Channa striata* extract at the concentrations of 25%, 50%, and 100%. The number of fibroblasts in the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50% and 100% was higher than in the control group. The highest number of fibroblasts was found in the treatment group receiving *Channa striata* extract at the concentration of 100% about 5.6 on day 3, but declined into 5.4 on day 5 and 4.8 on day 7 as seen in Table 1 and Figure 1. Based on Table 3, 5 and 7, the number of fibroblasts decreased on days 5 and 7. This finding is consistent with a theory stating that fibroblasts will first appear on day 3. The decline in the number of fibroblasts can also be associated with re-epithelization process of mucosal ulcer healing in Wistar rats on day 7.[12]

The number of fibroblasts increased in the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100%. This is because *Channa striata* extract contains copper (Cu). Izzati *et al.*[18] reported that *Channa striata* extract contains 0.447 mg/ L of CU. Copper plays a role in the growth and replication of cells that can trigger the proliferation of fibroblasts in areas that experience healing process. Besides copper, FGF-2 expression can also increase, triggering the proliferation of fibroblasts and the expression of collagen type 1. As a result, the proliferation of fibroblasts increase, so they can repair tissue structures faster during the wound healing process.

The expression of FGF-2 in the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100% declined from day 3 to day 7. However, the expression of FGF-2 generally increased in the treatment groups receiving *Channa striata* extract at the concentrations of 25%, 50%, and 100% as shown in Table 2 and illustrated in Figure 4 as well as proved by statistical significance values in Table 4, Table 6, and Table 8. Similarly, the researches conducted by Soepribadi[6] and Nagayasu-Tanaka[7] show that the expression of FGF-2 will increase immediately after the injury, and reach its peak

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on day 3. This is because FGF-2 which stimulates the proliferation of fibroblasts has been reduced, but the amount of collagen will continue to increase until the fourteenth day. It also affects the amount of collagen expression since FGF accumulates collagen.

Based on the data obtained, *Channa striata* extract has effects on the number of fibroblasts and the expression of FGF-2. Similarly, the researches conducted by Restiana *et al.* and Soemaridini *et al*. show that *Channa striata* plays a role in wound healing process due to the high albumin level contained in the fish.[13,14] Thus, *Channa striata* extract at a concentration of 100% indicates that there are 7.568 mg/ L of albumin, 6.7 mg/ L of Zn, 0.72 mg/ L of Fe, and 0.447 mg/ L of Cu.[18]

Albumin is one type of protein. This protein plays a role in increasing the proliferation of fibroblasts, thus increasing the synthesis, accumulation, and remodeling of collagen. Albumin also plays a role in oxygen transport. zinc, moreover, plays a role in the growth and replication of cells. Zn also plays a role in immune response. Cu serves to improve angiogenesis process through increased expression of VEGF and FGF-2. Fe plays a role in DNA replication. Fe also plays a role in the formation of collagen. In addition, Cu is reported to increase VEGF triggering the increasing of angiogenesis.[13-15] In the other researches, copper is also reported to increase FGF-2 that plays a role in the proliferation of fibroblasts and the expression of collagen type 1, thus, the repairing process of tissue structure and the process of wound healing can be accelerated.[16,17]

However, this study still has several limitations. This research still cannot be able to determine the total number of active substances contained in *Channa striata* extract at a concentrations of 25%, 50%, and 100% affecting the number of fibroblasts and the expression of FGF-2. This research also still cannot determine the standardization of *Channa striata* quality and its extract quality affecting the number of fibroblasts and the expression of FGF-2. In coclusion, *Channa striata* extract increased the fibroblasts number and FGF-2 expression in mucosa wound healing process.

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