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RESEARCH ARTICLE

Effect of aloe vera on the proliferation phase of oral mucosal wound healing in rats

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ABSTRACT

Aloe vera is known as a medicinal plant containing an active substance acemannan thought to play a role in accelerating wound healing. This study aims to determine the effect of aloe vera extract on the proliferation phase of oral mucosa wound healing in rats by looking at epithelial thickening, epithelial gaps closure, growth of new blood vessels, and connective tissue growth. This research is a pure experimental study with a post-test only control group design. On the left buccal mucosa of the mouth of 24 white Wistar rats (n = 24), an incision was made by scalpel with 10 mm length and 2.5 mm depth. The rats were divided into 4 groups: groups 1 and 2 as controls, while groups 3 and 4 were applied with aloe vera extract made by maceration technique. Wound tissue was observed histologically with Hematoxylin-Eosin staining under a microscope with an image analyzer for measuring the thickness of epithelium. The analysis of epithelial gap width used morphometry, and the number of capillaries was counted manually. Connective tissue thickness was measured with Image-J software. These were carried out on days 7 and 14 after treatment and the data were analyzed with the independent t-test and Mann-Whitney test. The results showed that aloe vera extract had no significant effect on epithelial thickening on day 7 ($p = 0.701$) nor on day 14 ($p = 0.639$), but a significant effect was shown on epithelial gaps closing ($p = 0.049$), connective tissue thickening ($p = 0.004$), and capillary increase on day 7 ($p = 0.049$). It could be concluded that aloe vera extract could potentially accelerate the epithelial gaps closure, connective tissue thickening, and capillary increase during the proliferation phase of the oral mucosa wound healing.

Keywords: aloe vera extract; epithelialization; wound healing; mucosal tissue; angiogenesis

INTRODUCTION

The oral cavity is lined with oral mucosa, which protects the tissues in the oral cavity.[1] The oral mucosa consists of stratified squamous epithelium and a layer of connective tissue (lamina propria).[2] Epithelial cells are mostly keratinocytes which differ from lamina propria, a loose connective tissue formed beneath the epithelium consisting of fibroblasts, lymphocytes, macrophages, leukocytes, eosinophils, mast cells, plasma cells, and small blood vessels.[3] The presence of trauma, temperature, chemical, and electrical substances can cause injury to the mucosa.[4]

When an injury occurs, the body provides a physiological response in the form of bleeding, contraction of blood vessels, inflammatory response, and then a healing process occurs.[5] Increased wound healing can be seen from the thickness of the epithelium, granulation tissue, angiogenesis, fibroblast cell density, collagen fibers, and wound contraction.[5] The faster the re-epithelialization takes place, the faster the epithelial structure of the oral mucosa reaches a normal state.[6] In the proliferative phase, angiogenesis, granulation tissue formation, collagen deposition, epithelialization, and wound retraction occur.[5]

Aloe vera is one of natural ingredients known to be useful in wound healing.[7] Aloe vera is usually used to promote hair growth and helps wound healing.[8] Aloe vera contains many active substances including saponins, flavonoids, tannins, and polyphenols that are very useful in accelerating wound healing. Aloe vera can also stimulate epidermal growth factors, improve fibroblast function, and the formation of new blood vessels which can accelerate wound healing

and closure.[1] The contents of aloe vera such as acemannan and β-sitosterol are also thought to accelerate the process of angiogenesis.[9]

Several studies on aloe vera have been conducted. Budiyanto's research on the healing of decubitus wounds in white rats showed that the administration of aloe vera extract with concentrations of 50% and 100% could accelerate wound healing.[10] Research by Rahayu, et al on the effect of topical administration of aloe vera gel on re-epithelialization of the epidermis in mice skin cuts found that there was an increase in the thickness of re-epithelialization in the aloe vera gel group compared to the untreated group and the NaCl 0.9% group. Listari and Hasanah conducted a study on the effect of aloe vera gel on the number of blood vessels after gingivectomy. The results showed that the number of blood vessels increased in the group given aloe vera.[11] Considering the findings of these researches, this study aimed to determine the effect of aloe vera extract on accelerating wound healing process as seen from the proliferation of epithelial cells, angiogenesis, and connective tissue repair in the oral mucosa using white mouse models.

MATERIALS AND METHODS

This research is pure experimental research with post-test only control group design. This research was carried out at the Phytochemical Laboratory of the Faculty of Pharmacy, University of Sumatra Utara, and the Biology Laboratory of Universitas Negeri Medan. Research permits and ethics approval were obtained from the Ethics Committee for Health Research Implementation at the Faculty of Medicine, University of Sumatra Utara.

In this study, 6 white male rats aged 2-3 months with a body weight of 100-150 grams were used for each treatment group, so the total number of subjects was 24 (n = 24). The selected rats had a complete number of teeth (16 teeth) with healthy conditions characterized by active movement, clean, no significant hair loss, had never received any previous treatment and no abnormalities.

The subjects were divided into 4 treatment groups. Group 1 was without treatment and was examined on the 7th day. Group 2 was without treatment and was examined on day 14. Mucosal samples in group 3 were smeared with aloe vera extract and were examined on the 7th day. In group 4, the mucosal samples were smeared with aloe vera extract and this group was examined on the 14th day. Adaptation time of all test animals lasted 7 days prior to the treatment. They were placed in separate cages according to their treatment group which were lined with husk and covered with wire gauze. Rats were fed (hi-gro 551) and given water 3 times a day.

An incision was made on the rat's left buccal oral mucosa with a length of 10 mm and a depth of 2.5 mm using a sterile no. 10 knife and a no. 3 scalpel. The blood that came out was cleaned with 0.9% NaCl using a 5 ml syringe until the bleeding stopped and dried with sterile gauze.

The aloe vera plant used was fresh, healthy, and free from pests. The aloe vera extract was made by maceration technique. A total of 5 kg of aloe vera was washed with running water and cut into pieces. They were then dried at 40 ^{o}C for 7 days in a drying machine. After the aloe vera was dry, it was blended into powder and soaked in 96% ethanol as high as 1 cm above the sample surface for 3 x 24 hours, and stirred occasionally. The immersion results were filtered using a Büchner funnel lined with filter paper. The results of the filtration were evaporated using an IKA rotary evaporator type RV OS-ST IP-B at 40-50 ^{o}C to obtain a thick extract.

Groups 1 and 2 were not given any treatment. In groups 3 and 4, aloe vera extract was applied to the wound twice a day (morning and evening) for 14 days. In groups 1 and 3, left oral mucosal tissue with a size of 0.5 x 1 cm was taken from dead mice on the 7th day and put into a pot containing formalin buffer solution. In groups 2 and 4, the oral mucosal tissue of the dead mice was taken on day 14.

The epithelium of the left buccal oral mucosa was treated with histological staining using Hematoxylin-Eosin (HE) on glass slides and observed using a microscope equipped with

an image analyzer with a magnification of 200x. Re-epithelialization measurement was based on the epithelial thickness and epithelial gaps width. The measurement of new epithelium (epithelial thickness) in the wound area was carried out by measuring the farthest distance (maximum thickness) and the shortest distance (minimum thickness) measured from the lowest boundary of the basal cell layer to the outermost layer of superficial cells. The result of the measurement of the thickness of the epithelial layer was obtained from the sum of the maximum and minimum thickness and then divided by two. Meanwhile, the epithelial gaps width measurement was carried out using the morphometric method, which measures variations and changes in the shape and size of an organism's body. Epithelial thickness and wound closure width were measured using a micro-ruler on a microscope (in micrometers (μm)).

The oral mucosal tissue that was injured was taken and treated with histological staining. It was seen under a microscope with 400x magnification and 5 visual field areas of each part were observed. The number of capillaries was counted manually by observing the preparations under a microscope and the results of the calculations were recorded by the observer. Capillary blood vessels were seen in the basal lamina and with size 9-12 μm. These were larger than red blood cells and they were surrounded by a single layer of endothelial cells in their walls. The observer has been calibrated in relation to the standard calculations that will be performed.

The observation of the histology of the mucosal tissue used a light microscope with 100x magnification. Furthermore, the thickness of the connective tissue was measured on the 7th and 14th day using Image-J software.

The data obtained in this study were analyzed using the Paired Sample t test to compare the difference between the two means of two paired samples with the assumption that the data were normally distributed. Furthermore, to determine whether or not there was a difference in mean between two unrelated sample groups, the independent sample t test was carried out. In this study, the Kruskal-Wallis test was also carried out to determine whether there were statistically significant differences between two or more groups of independent variables on the dependent variable on a numerical data scale. The Mann-Whitney test was used to determine the difference in the average of the two unpaired groups.

RESULTS

The results of the histopathological examination showed that overall the treatment group that was smeared with aloe vera extract had a higher average thickness of the epithelium than the control group on day 7 and day 14. On day 14, the treatment group that was smeared with aloe vera extract had the highest average thickness of the epithelium of 40.87 μm. The average thickness of the epithelium showed that aloe vera extract had an effect in accelerating the wound healing process (Table 1).

On day 7, the average thickness of the epithelium in the control group was 26.56 μm, while for the treatment group was 31.28 μm. Statistically it can be concluded that there is a difference in the average thickness of the epithelium but not significant with p-value = 0.495 ($p > 0.05$) between the control group and the treatment group. Of all the existing average differences, the highest average difference (at 14.31 μm) occurred on the 14th day for the treatment group and on the 7th day for the control group. Based on the microscopic histopathological examination, on the 7th day post-injury the control and the treatment groups were coated with keratin on top of the epithelial tissue (Figure 1). Microscopic observation on the 14th day revealed that the epithelial tissue in the control group and the treatment group was almost the same as the surrounding tissue and rete peg/ papillae began to form.

The treatment group that was smeared with aloe vera extract had a smaller average width of the epithelial cleft than the control group on the 7th and 14th days. On day 14, the treatment group had an average epithelial cleft width of 0 μm (completely closed). The results of the average width of the epithelial cleft showed that aloe vera extract had

Table 1. The results of the examination of the average epithelial thickness and clefts in the oral mucosa of a white mouse model

No.	Group	Epithelial thickness check			Epithelial cleft examination		
		± SD (μm)	Mean Difference	P-Value	± SD (μm)	Mean Difference	P-Value
1	3 (Treatment 7th day)	31.28 ± 17.35	4.72	0.701	7.91 ± 19.37	27.28	0.049*
	1 (Control 7th day)	26.56 ± 23.52			35.19 ± 31.46		
2	3 (Treatment 7th day)	31.28 ± 17.35	2.84	0.752	7.91 ± 19.37	8.83	0.416
	2 (Control 14th day)	31.12 ± 9.43			16.74 ± 29.47		
3	3 (Treatment 7th day)	31.28 ± 17.35	9.59	0.509	7.91 ± 19.37	7.91	0.317
	4 (Treatment 14th day)	40.87± 29.60			0		
4	4 (Treatment 14th day)	40.87 ± 29.60	14.31	0.376	0	35.19	0.007*
	1 (Control 7th day)	26.56 ± 23.52			35.19 ± 31.46		
5	4 (Treatment 14th day)	40.87 ± 29.60	6.75	0.639	0	16.74	0.104
	2 (Control 14th day)	34.12 ± 9.43			16.74 ± 29.47		

Independent Samples t-test, *significancy p < 0.05

an effect on accelerating wound healing by closing the width of the epithelial cleft in the oral mucosal wound area of the white rats (Figure 2).

Furthermore, the width of the mucosal epithelial cleft on day 7 (Table 1) showed a significant mean difference (p = 0.049) between the control group and the treatment group smeared with aloe vera extract. The highest difference in the width of the epithelial cleft was found in the treatment group smeared with aloe vera extract on the 14th day and the control group was on the 7th day with 35.19 μm. The lowest was in the treatment group smeared with aloe vera extract on the 7th day, while the control group was on day 14 with 8.83 μm (Table 1).

The results of the microscopic observations showed that there was an epithelial cleft in the control group and the treatment group with aloe vera extract on the 7th day post-injury. Meanwhile, on the 14th day post-injury, the epithelial clefts were getting smaller in the control and treatment

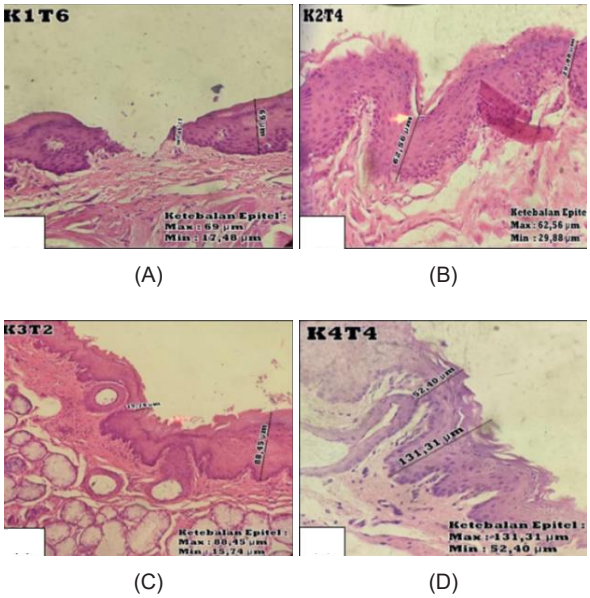

Figure 1. Histopathological description of changes in the thickness of the oral mucosal epithelium with a white mouse model stained with Hematoxylin-Eosin with 200x magnification; (A) group 1 (control day 7), (B) group 2 (control day 14), (C) group 3 (after 7 days of administration of aloe vera extract), (D) group 4 (after 14 days of administration of aloe vera extract)).

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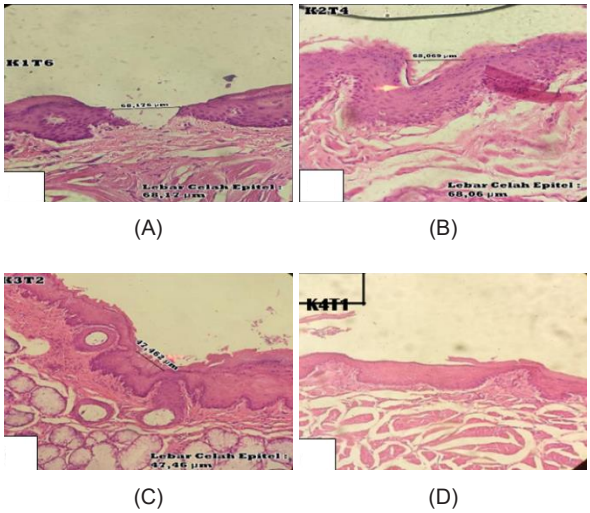


(A) (B)

(C) (D)

Figure 2. Histopathological description of changes in the oral mucosal epithelial cleft with a white mouse model stained with Hematosilin-Eosin with a magnification of 200x; (A) group 1 (control day 7), (B) group 2 (control day 14), (C) group 3 (after 7 days of administration of aloe vera extract), (D) group 4 (after 14 days of administration of aloe vera extract)).

groups. However, the epithelial cleft closure that occurred in the control group was not as fast as the treatment group given aloe vera extract (Figure 2).

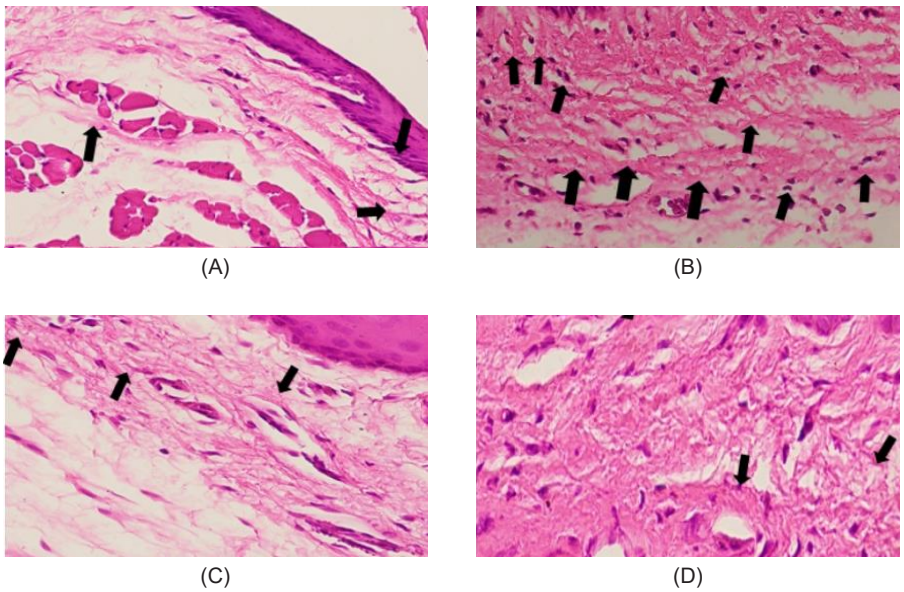
The results of the examination of the oral mucosal connective tissue samples showed that the average value of the thickness of the connective tissue in the control group on the 7th day was 1.68 µm, while the average value in the treatment group was 0.80 µm. On day 14, the thickness of the connective tissue in the control group was 1.05 µm, whereas in the treatment group the average value was 0.85 µm. This indicates a decrease in the thickness of the connective tissue after administration of aloe vera extract.

Table 2. Differences in connective tissue thickness on day 7 and day 14 with several statistical tests

No.	Variable	Connective tissue thickness		
		N	Mean ± SD (µm)	p-value
1	Day-7 (Control)	6	1.68 ± 0.526	0.004*
	Day-7 (Treatment)	6	0.80 ± 0.252	
2	Day-14 (Control)	6	1.05 ± 0.554	0.488
	Day-14 (Treatment)	6	0.85 ± 0.393	

T-independent test, *Significancy p < 0.05

The results of the analysis using the independent T test (Table 2) showed that there was a significant difference in the thickness of the connective tissue between the control group (p = 0.004) and the treatment group on day 7.



(A) (B)

(C) (D)

Figure 3. Histopathological description of blood capillaries on the oral mucosa of rats with 400x magnification. Arrows indicate capillaries; (A) Control group on 7th day, (B) After 7 days of administration of aloe vera extract, (C) Control group on day 14th, (D) After 14 days of administration of aloe vera extract.

Meanwhile, on day 14, there was no significant difference in the thickness of the connective tissue between the control group and the treatment group (p = .488). From the data analysis using the Kruskal-Wallis test, it was found that there was a significant difference in the thickness of the connective tissue between groups 1, 2, 3 and 4 (p = 0.022).

The results of the histopathological examination showed that on the 7th day, the average number of capillaries in the control group was 11.8, while in the treatment group was 22.3. The results of the Mann-Whitney test showed that there was a significant difference in the number of blood vessels between the control and treatment groups on day 7 (p = 0.049). On day 14, the average number of blood vessels in the control group was 15.0 and in the treatment group it was 13.6 (p = 0.14).

Figure 3 shows the addition of capillary blood vessels in the sample given aloe vera extract. The tissue shown in the image consists of epithelium and connective tissue with blood capillaries.

DISCUSSION

The results of this study showed that aloe vera extract applied for 14 days was shown to give the most effective results in helping accelerate the process of epithelial thickening and sealing of epithelial gaps in oral mucosal wounds. This is in accordance with the results of a study conducted by Ningsih et al regarding post-extraction wounds which showed that the re-epithelialization of the wound reached approximately half of the wound surface on day 7 and the epithelium in all samples of the treatment group had covered the entire wound surface on the 14th day.[12] In Hajashemi's research, the administration of aloe vera gel showed significant healing in incisional wounds in Wistar rats.[13] In his research, Mustaqim suggested that the administration of aloe vera could repair mucosal damage by triggering fibroblast growth factor receptors.[14] The increase in the thickness of the epithelium may be due to the resultant effect of all the active substances contained in aloe vera gel: mannose, glucomannan, krisofan acid, acemannan, vitamin A, vitamin C and vitamin E. Acemannan is a complex carbohydrate that can stimulate the production of growth factors in wound healing produced by keratinocyte growth factor (KGF), a member of fibroblasts.[15] KGF can increase re-epithelialization and accelerate wound closure. Vitamin A and vitamin E also increase re-epithelialization by increasing blood flow to damaged cells, thereby accelerating the recovery of damaged epithelial cells.[16,17]

The results of the observations in this study also showed an increase in the epithelialization and narrowing of the epithelial gap in the group that was applied with aloe vera extract. Furthermore, the treatment group that was smeared with aloe vera extract had a wide epithelial cleft that was nearly completely closed when compared to that of the control group that was not smeared with aloe vera extract. Teplicki et al who examined the effect of aloe vera on wound healing found that aloe vera had significant stimulatory effect on cell proliferation and migration of fibroblast and keratinocytes.[18] The results of Kalangi's research showed a faster reduction in wound diameter when given aloe vera.[19]

The 7-day treatment group and the 14-day treatment group did not experience a significant difference in connective tissue thickening. This is probably due to a healing process that is supported by the nutritional content of aloe vera. In the treatment group, the connective tissue became thinner due to a longer maturation phase. At this stage the irregular collagen fibers were destroyed and replaced with new collagen fibers that were oriented to better withstand the tensile forces of the wound.[20] In addition, this study showed that the connective tissue in the treatment group became thinner. This is probably due to a decrease in wound metabolism followed by a decrease in vascularity and an increase in wound contraction resulting in a decrease in the size of the wound. This indicates that aloe vera extract may have the ability to accelerate wound closure through re-epithelialization process.[19]

The main process of fibroblast growth will occur by days 7 to 14 after injury and after that it

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will continue to improve until the skin structure returns to normal. The growth of connective tissue was more prevalent in the treatment group. The density of the connective tissue helped contract the wound, and as a result the edges of the injured skin were pulled and the width of the wound became smaller. This could be seen on the 7th day in the treatment group where the wound had a high tissue density value and when viewed pathologically the anatomical width of the wound had narrowed because the wound had more connective tissue. The greater the wound contraction power, the greater the edges of the wound would be gripped and pulled, causing a large wound to become smaller. On the 7th and 14th days, the control group with the treatment group was very different from the control group with a dense amount of connective tissue, but there were still some empty parts. This shows that the administration of aloe vera extract may further increase the formation of connective tissue in the wound.[18]

The results of this study showed that the average number of capillaries in the group given aloe vera extract was higher than the control group on day 7. On the 7th day in the treatment group, the highest number of blood vessels was 22.3 (±SD 16.9). The results of this study are in line with the results of Listari and Hasanah's research which suggested that there was an increase in the number of blood vessels in the group given topical aloe vera gel.[11] The content of β-sitosterol in aloe vera extract can stimulate endothelial cell migration and angiogenesis, and can promote blood clots to accelerate wound healing process.[9] Aloe vera has the active compound acemannan which can stimulate cell proliferation and activate macrophages that produce growth factors such as VEGF and FGF. VEGF degrades the extracellular matrix around endothelial cells, promotes proliferation and migration of endothelial cells, and helps in the formation of blood vessel structures. FGF increases the reendothelialization process in blood vessels that are damaged by endothelial cells.[21]

On the 14th day the number of capillaries was less than that on the 7th day. This was probably because the newly formed blood vessels started to stabilize and decreased in number as the extracellular matrix began to fill the missing areas due to the treatment. In this study, the treatment group showed a significantly faster wound closure than the control group on day 7. Ruauw's research found that the wounds on the mucosa which was given aloe vera extract closed on the 8th day, while the wound in the control group closed on the 12th day. In this study, the wound given aloe vera in the treatment group was completely closed on the 14th day and the mean number of capillaries had decreased by 13.6. This was because the proliferative phase had stopped, which was marked by the fusion of epithelial cells and the closure of the entire wound surface. With the wound surface closed, the next phase is the remodeling phase. Angiogenesis is absolutely necessary when an injury occurs because it delivers nutrients and oxygen and maintains the continuity of the function of various tissues and organs.[21]

Based on the results of this study, it is not clear which active compound has the highest impact on the formation of angiogenesis, as well as the toxicity of aloe vera. Therefore, further research is needed to obtain more comprehensive knowledge about the effect of aloe vera on wound healing process. Research on the effect of giving aloe vera extract on wound healing has been carried out according to the proper procedure, but there are still some limitations in its implementation.

CONCLUSION

Aloe vera extract can accelerate the formation of epithelial thickness and closure of wound gaps. Administration of aloe vera extract has resulted in thinner connective tissue in wound during the healing process. Meanwhile, in the process of angiogenesis, the administration of aloe vera extract can promote the formation of new blood vessels to accelerate the wound healing process.

CONFLICT OF INTEREST

The authors declare no conflict of interest with the data contained in the manuscript.

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