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Administration of Oral Gemitir Flower Extract (*Tagetes Erecta L*) Increased The Number of Neovascularization, Fibroblasts Cell and Epithelization of Wound in Male Wistar Strains Rats (*Rattus Norvegicus*)

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ABSTRACT

Background: Herbal ingredients that can be used to reduce wound healing on the skin are the administration of bioactive compounds from gemitir flowers (*Tagetes erecta L)* used as an anti-inflammatory and antioxidant. This study prove that oral gemitir extract increases the number of neovascularization, fibroblast cell and epithelialization of wound healing in male Wistar strains rats. ***Method:*** This research is anexperimental research with a randomized posttest-only control group design method. The research subjects used 28 male Wistar rats (*Rattus norvegicus*), which were divided into 2 control groups and 2 treatment groups. The analytical method used the Shapiro-Wilk Test and Levene's Test and then compared using the one-way ANOVA post hoc with least significant difference (LSD). ***Results:*** Neovascularization P0-4 and P0-14 have the same value 1.86±0.90,while in group P1-48.86±1.35and P1-14 decreased to 5.00±1.15. Number of P0-4 fibroblast cells: 8.29±3.25and P014:9.00±3.51cells/field of view, while PI-4:18.57 ± 4.89 and P1-14: 32.00 ± 7.39. Epithelialization results as described by epithelial thickness at P0-4: 28.08 ± 10.07 µm and P0-14:298.86±273.88µm, while at P1-4: 1096.71±133.93µm and P1-14: 1674.00± 331.55µm. The results of the one way ANOVA $p<0.001$. LSD group P0 (4) vs P0 (14) were not significantly different while P0 (4) vs P1 (4), P0 (4) vs P1 (14), P1 (4) vs P1 (14) all differed significantly with $p<0.05$. ***Conclusion:*** Oral administration of ethanol extract of gemitir flowers increased neovascularization in wound healing male Wistar rats on day 4 and increased the number of fibroblasts and thickness of epithelialization on days 4 and 14.

Keywords: gemitir flower (*Tagetes erecta L*); neovascularization; fibroblasts; epithelialization (thick epithelial epidermis); wounds

INTRODUCTION

Wound is network damage skin Which caused by contact physique (with source hot), intervention medical or change condition physiological. Moment happen wound, body do process healing wound in a manner experience through function biocellular And biochemistry Which continuous.[1]

Healing wound consists from three phase, that is inflammatory phase (0-3 day), formation phase network Which often called proliferative phase (3-14 day), And phase maturation network (remodeling), which can started (on the 8th day until 1 year).[2] Wide surface wound And depth wound depend on effectiveness maintenance wound as well as there nope complications Which hinder healing wound in a manner experience. Process healing wound long can cause disturbance on process repair network, like on patient carry on age, therapy steroids, sufferer diabetes And cancer.[3]

One material herbs accelerate healing wound on skin is gift compound bioactive from plant is (*Tagetes erecta l*), Which used as antioxidants anti inflammation.Gemitir flower is plant from family Asteraceae Which spread in whole world in various species And often used as plant ornamental. Flower gemitir This is known contain compound carotenoids like lutein, Beta carotene, alpha-carotene, zeaxanthin, anthrax athin And alpha-cryptoxanthin.Flower yellow contain flavonoids And carotenoids in amount big Because lutein is pigment yellow, but compound carotenoids Which found on plant Still form ester carotenoids.[4]

In relation to the wound healing process, flavonoids can increase the levels of transforming growth factor-beta (TGF-β) at the wound site and their effects begin to show on the 4th and 5th day of examination.[5]TGF-β has previously been shown to be an important factor that triggers fibroblast proliferation in the wound healing process.[6]Flavonoids can increase levels of vascular endothelial growth factor (VEGF), which is one of the factors involved in the process of stimulating the formation of new blood vessels in the wound healing process.[5]

Flavonoids have been shown to increase migration and proliferation of epithelial cells, as well as formation, increase migration and activity of myofibroblasts.[7] Flavonoids can increase epithelialization and formation of granuloma tissue in wounds, due to increased collagen production and angiogenesis in wounds.[8,9] Based on data in on, researcher do study for clarify that gift extract ethanol flower gemitir (*Tagetes erecta l*) in a manner orally can speed up healing wound on mouse male strain Wistar (*Ratus norvegicus*) test.

METHOD:

Study experimental randomized post test only control group designwhich was carried out at the Integrated Biomedical Laboratory Unit, Faculty of Medicine, Udayana University.Deep sampleIn this study, male white rats (*Rattus norvegicus*) aged 2-3 months, weighing 180-300 grams in good health. The research subjects used 28 male Wistar rats (*Rattus norvegicus*), which were divided into 2 control groups and 2 treatment groups. The control group was divided into 2 groups into 4 days group (P0-4) and 14 days group (P0-14). The treatment group was also divided into 2 groups, namely the 4 day group (P1-4) and the 14 day group (P1-14) so that the total sample was 28 individuals. The control group was given distilled water (placebo), while the treatment group was given 2 mL of gemitir flower ethanol extract orally twice a day. The analytical method used the Shapiro-Wilk Test and the Levene Test and then compared using the one-way ANOVA test post hoc least significant difference(LSDs).

The ethanol extract of Gemitir Flowers (*Tagetes erecta l*) was made at the Laboratory of the Faculty of Agricultural Technology, Udayana University, Bali.

The procedure for making gemitir flower ethanol extract (*Tagetes erecta l*) is as follows:

(1) Flower Gemitir 1 kg taken from the Badung market in Bali.
(2) Flowers that have been washed clean and then dried within the ovenfor 24 hours at 50°C.
(3) The dried flowers are ground using a disc mill until it becomes powder.
(4) Then macerated in solvent 96% (ethanol) during 48 O'clock For remove material active from material Which can extracted.
(5) The filtrate is obtained by filtering through 4 layers of clothgauzefollowed by filtering using Whatman filter paper no.1.
(6) The filtrate obtained laterevaporatedusing a vacuum

All rats were made the same wound with Disposable punch biopsy, with a size of 3 mm, then divided into 4 groups and given treatment. After the intervention of anesthetized rats, skin tissue was taken and histopathologically prepared preparations were then assessed for the number of fibroblasts, neovascularization, and epithelialization of the epidermis.

RESULTS

Data studies variable neovascularization, amount cell fibroblasts, And epithelialization on each group treatment analyzed according to characteristics physiological And pathological skin. Results analysis neovascularization, amount cell fibroblasts And epithelialization on every group showed on Table 1.

TABLE 1: Mean Value of Variables Between Groups.

Variable	Group	Average	Standar Deviation	Median	Minimum	Maximum
Neovascularization						
4th day	P0 (4)	1.86	0.900	2	1	3
	P1 (4)	8.86	1.345	9	7	11
14th day	P0 (14)	1.86	0.900	2	1	3
	P1 (14)	5.00	1.155	5	4	7
Fibroblast count						
4th day	P0 (4)	8,29	3,251	8	4	13
	P1 (4)	18.57	4,894	18	12	25
14th day	P0 (14)	9.00	3,512	9	5	14
	P1 (14)	32.00	7,394	30	25	47
Epithelial thickness						
4th day	P0 (4)	257.96	150,900	230.80	103	524
	P1 (4)	1096,71	133,935	241.00	166	523
14th day	P0 (14)	298.86	273,875	977.00	759	1551
	P1 (14)	1674.00	331,545	1784.00	973	1965

This comparability analysis aims tocompareneovascularization rate, fibroblast cell count and epithelialization between the control group (P0) and the treatment group (P1). The results of this study were that the data were normally distributed and the data variants were homogeneous so that the significance analysis was tested by one way ANOVA test (Table 2) followed by an analysis test.post hoc with Leasts Significant difference (LSD) test (Table 3).

TABLE 2: Comparative Analysis of Each Variable between Groups with the One Way Anova Test.

Variable	Group	Average	p value	F	Overall p-value
Neovascularization					
4th day	P0 (4)	1.86±0.90	<0.001	57,61	<0.001
	P1 (4)	8.86±1.35			
14th day	P0 (14)	1.86±0.90	<0.001		
	P1 (14)	5.00±1.15			
Number of Fibroblasts/field of vision					
4th day	P0 (4)	8.29±3.25	0.001	33,77	<0.001
	P1 (4)	18.57±4.89			
14th day	P0 (14)	9.00±3.51	<0.001		
	P1 (14)	32.00±7.39			
Epithelial Thickness (µm)					
4th day	P0 (4)	257.96±150.90	<0.001	64.99	<0.001
	P1 (4)	1096.71±133.93			
14th day	P0 (14)	298.86±273.88	<0.001		
	P1 (14)	1674.00±331.55			

The macroscopic appearance of the mice according to the treatment is presented in Figure 1-4, neovascular and histopathological results neovascularization bar chart in figure 5 and figure 6. histopathologyamount fibroblastsper field of view and bar charts in figures 7 and 8. Histopathology of epithelialization and bar charts of the average thickness of the epithelium in figures 9 and 10.

TABLE 3: Least Significant difference (LSD) test.

Variable	Group			Average difference	P value	CI 95%	
						Lower limit	Upper limit
Neovascular	P0 (4)	vs	P1 (4)	-7.00	<0.001	-8.20	-5.80
	P0 (4)	vs	P0 (14)	0.00	1,000	-1.20	1.20
	P0 (4)	vs	P1 (14)	-3,14	<0.001	-4.35	-1.94
	P1 (4)	vs	P0 (14)	-3.85	<0.001	-5.06	-2.65
	P1 (4)	vs	P1 (14)	3.86	<0.001	2.65	5.06
Fibroblasts	P0 (4)	vs	P1 (4)	-10.28	0.001	-15.84	-4.73
	P0 (4)	vs	P0 (14)	-0.71	0.793	-6,27	4.84
	P0 (4)	vs	P1 (14)	-23.7	<0.001	-29,27	-18,16
	P1 (4)	vs	P0 (14)	9.57	0.002	4.01	15,13
	P1 (4)	vs	P1 (14)	13,42	<0.001	7,87	18.99
Epidermis thickness	P0 (4)	vs	P1 (4)	-838.75	<0.001	-1100.77	-576.73
	P0 (4)	vs	P0 (14)	-40.89	0.750	-302.91	221,13
	P0 (4)	vs	P1 (14)	-1416.03	<0.001	-1678.05	-1154.02
	P1 (4)	vs	P0 (14)	797.85	<0.001	535,84	1059,88
	P1 (4)	vs	P1 (14)	577,28	<0.001	315,27	839.30

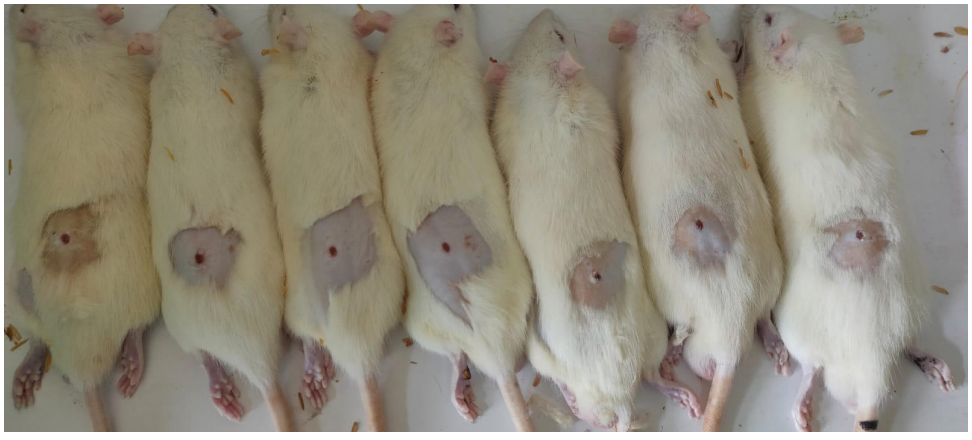

FIGURE 1: P0 mice (4).

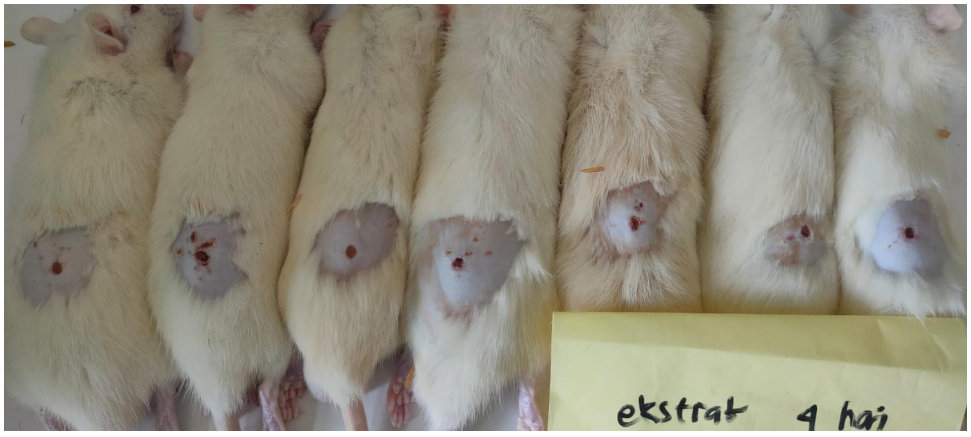

FIGURE 2: P1 Mice (4).

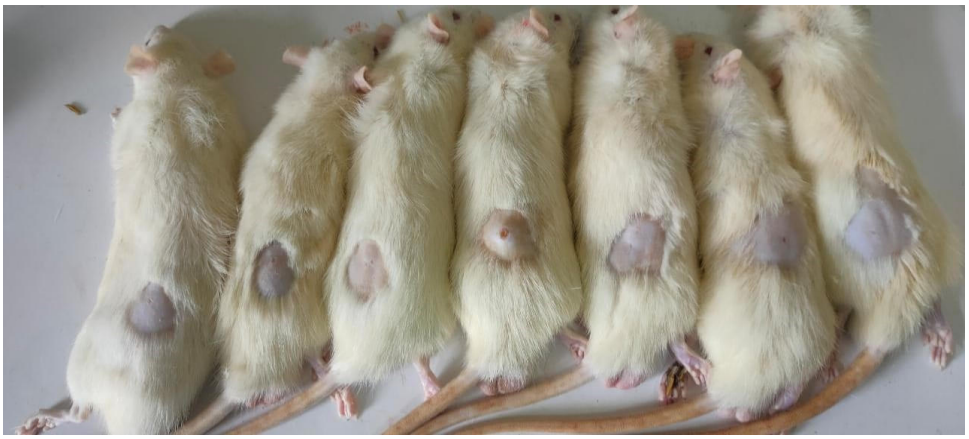

FIGURE 3: P0 Mice (14).

FIGURE 4: P1 Mice (14).

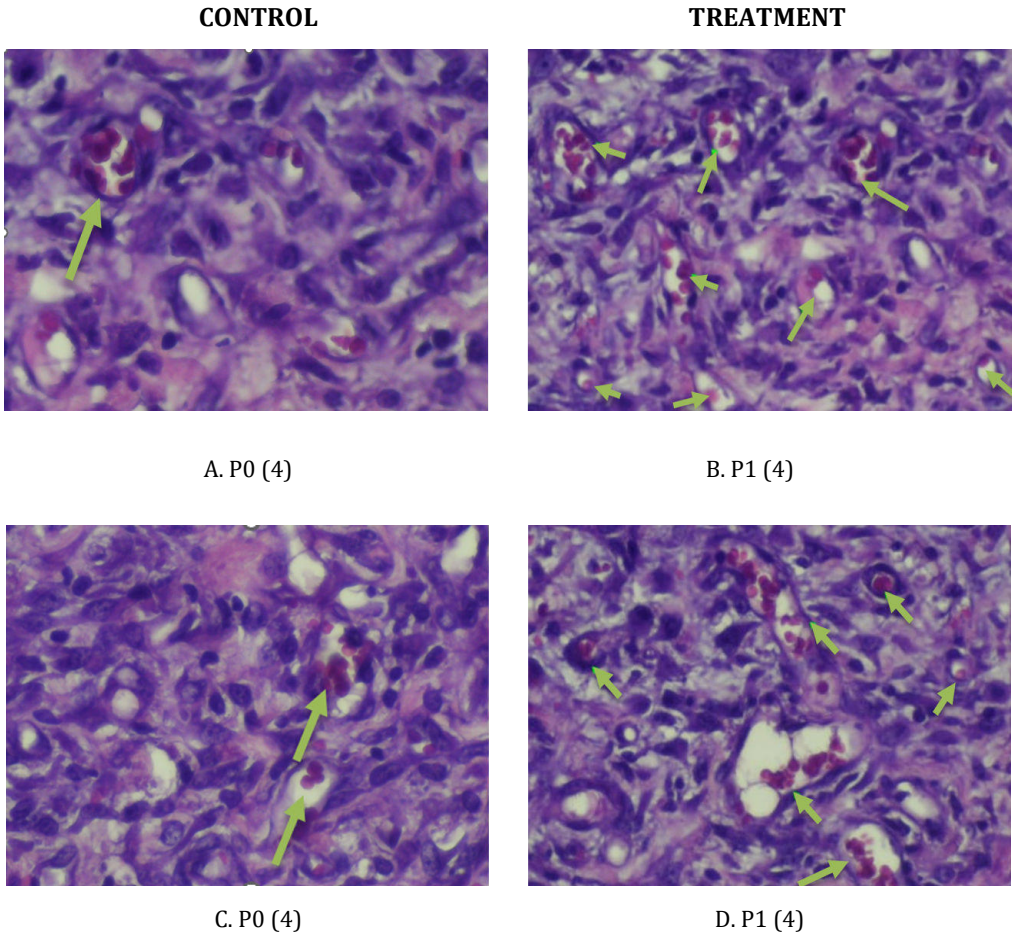

FIGURE 5: Histopathology of vascularization at 400x magnification, visible vascularization with a thin intima (green arrow), then counted the number of vessels in A. P01 was found to have 1 per field of view; B. P1 (4) found there were 8 per field of view; C. P0 (14) found 2 per field of view and D. P014 found 6 per field of view.

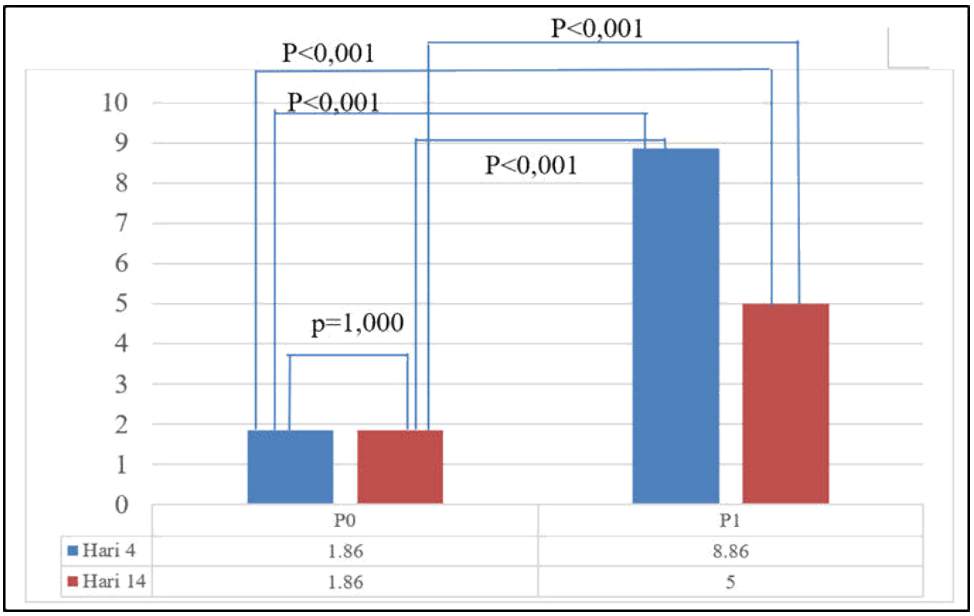

FIGURE 6: Bar chart of mean neovascularization per group.

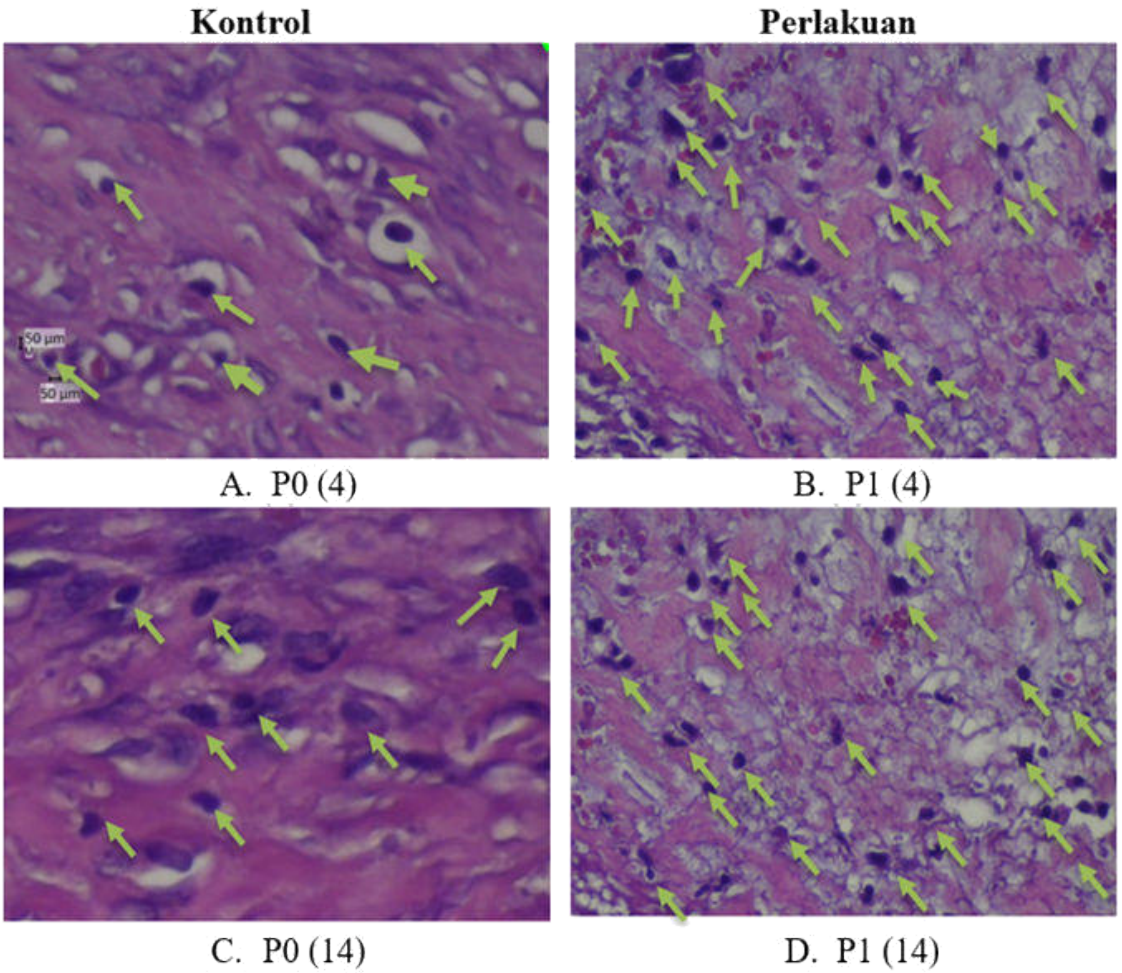

FIGURE 7: Histopathology of fibroblasts magnification 400x, shaped fibroblast cellsspindle(green arrow), then counted the number of A fibroblast cells. P0 (4) there were 7 per field of view; B P1 (4).

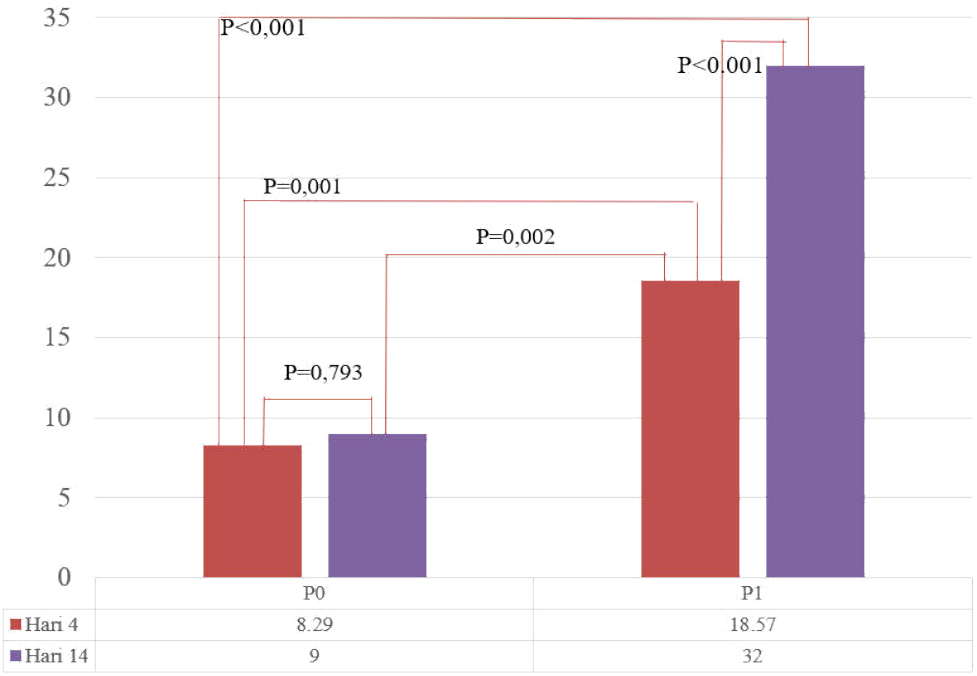

FIGURE 8: Average bar chartamount fibroblastsper field of view.

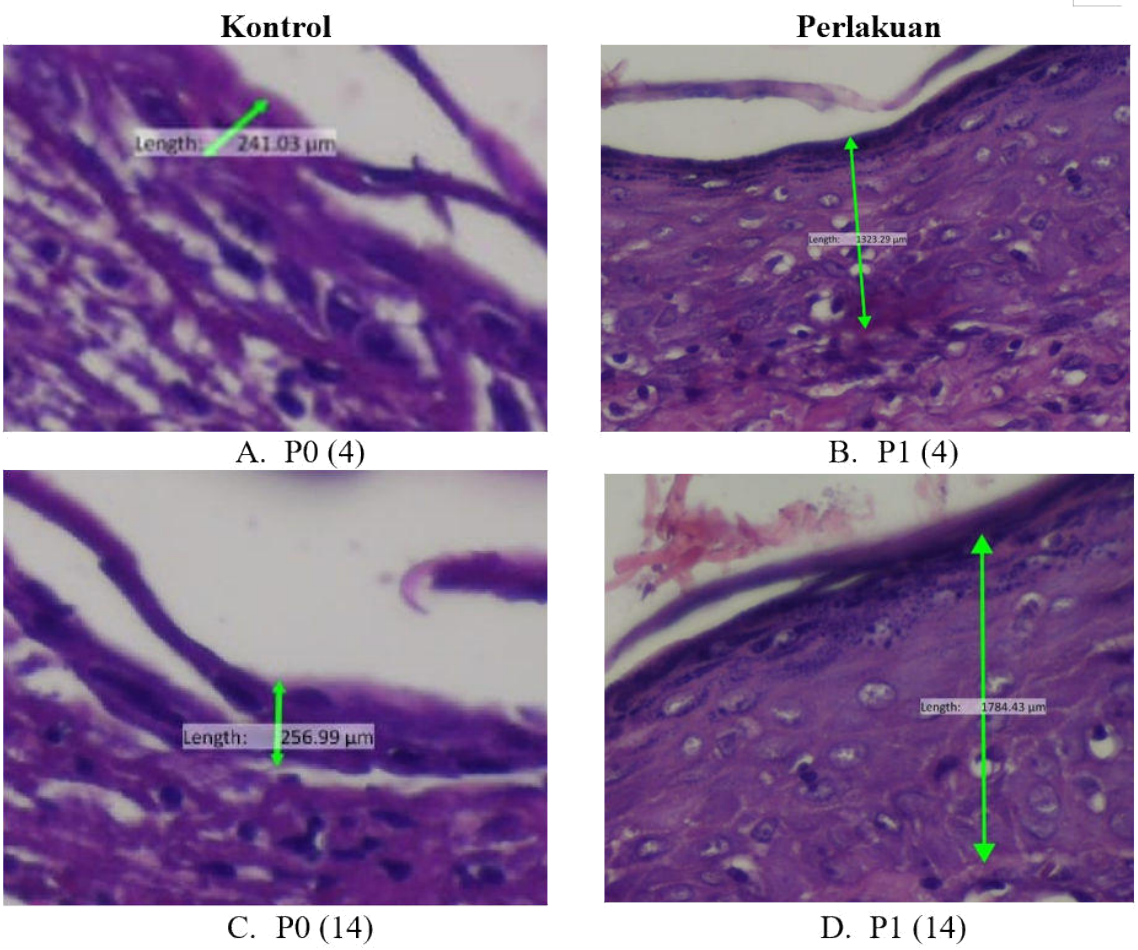

FIGURE 9: Histopathology of epithelialization at magnification 400x, found to be thick on A. P0(4) with a size of 241.03µm; B. P1 (4) with a size of 1323.29 µm; C P0(14) with a size of 256.99 µm and D P1(14) with a size of 1784.43 µm.

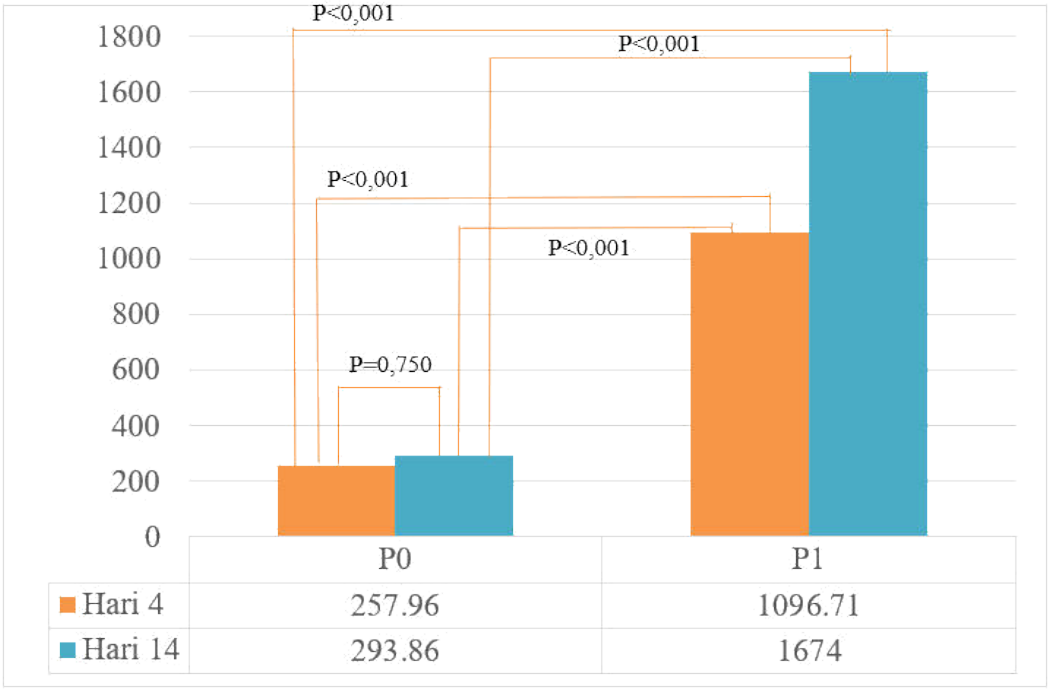

FIGURE 10: Epithelial thickness mean bar chart.

DISCUSSION

Oral gemitir flower extract (*Tagetes erecta l*) 2 mL 2 times in days has been shown to increase the number of neovascularization, fibroblasts and epithelialization in wound healing male wistar rats (*Rattus norvegicus*). Administration of gemitir flower extract from converted rats to humans is in accordance with that obtained in the dose conversion table.[10] Calculation of the dose conversion rate for 200 g rats = 56 for 70 kg humans, which means 168 mg x 56, so the dose for humans with a body weight of 70 kg is 9,408 mg or 9.4 g/day. Can be rounded up to 10 g/day or 2 tea spoons/day.

The results showed the mean neovascularization in the control group (P0) after given solution aquades 2 times a day during 4 days and 14 days the number of neovascularization was the same 1.86 ± 0.90,whereasin the treatment group (P1) after given gemitir flower extract orally every day for 4 days was 8.86 ± 1.35 and after 14 days the number of neovascularization was 5.00 ± 1.15. The results show that givingextractgemitir flower increased neovascularization on day 4 and decreased on day 14. Healing wound involve interaction going continuously between cell and matrix cell like observed in four phase healing wound. Which overlap overlapping, that is phase coagulation, phase inflammation, phase proliferation-migration and phase remodeling. Phase proliferation begins after response hemostasis and inflammation start subsided, healing wound started with angiogenesis, fibroplasia nd epithelialization. After phase inflammation end, happen neovascularization on area wound Which reach peak 3-5 day after injury and slowly decrease around day 7th.[11] This resulted in lower results after the neovascularization treatment on day 14 compared to day 4.

The number interaction between various type cell mediator cytokine and matrix extracellular happen in process healing wound. Fibroblasts the wound will develop breed And produce matrix collagen in amount big, Which help protect and repair network Which damaged.[12]

The number of fibroblast cells in the control group (P0) after being given the solutionaquades2 times a day for 4 days was 8.29 ± 3.25 and 14 days 9.00 ± 3.51 cells/field of view, whereas in the treatment group (P1) after being given gemitir flower extract orally every day for 4 days was 18, 57±4.89 and 14 days 32.00±7.39. These results indicate that the administration of gemitir flower extract for 4 days and 14 dayscanincrease the number of fibroblast cells in the healing processwound.

Epithelialization resultsdepictedby the thickness of the epithelium in the control group (P0) after administration of the solution aquades2 times a day for 4 days was 28.08 ± 10.07 and the 14 day group was 298.86 ± 273.88 µm, while in the treatment group (P1) gemitir flower extract orally every day for 4 days was 1096.71 ± 133 .93 µm and the 14 day group was 1674.00 ± 331.55 µm. Results flower Gemitir can improve epithelialization on process healing wound. Besides formation network granulation with deposition collagen and proteins network tie as well as angiogenesis, epithelialization is Wrong One step main in process healing wound.[12]

This study that gift extract gemitir flower in a manner orally can speed up healing wound. Matter content phytochemicals from gemitir flower that alone. Based on results screening phytochemicals flower gemitir contain flavonoids, tannins And saponins Which show that gemitir contain compound active metabolites secondary.[13] Gemitir flower extract has a high antioxidant capacity of 9469 mg/LGAEAC.

Antioxidants are molecules that can inhibit or stop oxidative damage that occurs by donating electron free radical molecules so that they can reduce the negative effects of these free radicals.[14] The antioxidant content in the ethanol extract of gemitir flowers (*Tagetes erecta l*) functions to fight free radicals.[4]

Gemitir flower has a flavonoid content of 6048.12 mg/100g. Flavonoids has proven increase migration and proliferation cell epithelium, as well as formation, migration, and activity fibroblasts.[7] Giving flavonoids with orally capable increase epithelialization and formation network granulation on wound. Enhancement epithelialization and network granulomatous on wound, possible caused by enhancement production collagen and angiogenesis on wound.[8,9,15] Process healing wound and show that flavonoids can stimulate mechanism which related with wound healing, also regeneration network.[16]

Flavonoids significantly increase speed wound healing processuse raise wound contraction rate, reducing moment epithelialization, collagen deposition,&induce granulation.[7] Content flavonoids as antioxidants antimicrobial and also role as anti-inflammatory on wound.[17]

Flower extract gemitir contain phenol in a sizeable amount of phenol 13179.07 mg/100 g GAE. Compound phenolic is most important from radical free and antioxidants plant.[18] A number of researcher has show that concentration compound phenolic on plant correlated positive with activity the antioxidants. Level compound phenolic more tall on plant show activity antioxidants.[7,9,15] Process healing wound, compound phenolic on gemitir flower extract can increase proliferation cell fibroblasts, compound phenolic increase process mitosis in culture cell fibroblasts mouse. Giving compound phenolic Also can increase migration fibroblasts and activity fibroblasts on network wound.[19,20]

Concentration compound phenolic Which tall on extract gemitir flower can speed up healing wound with increase production collagen cell fibroblasts on various type animal test, on wound operation and laceration.[21,22] Lots study find that content phenolic from material experience can speed up process healing wound through activity antioxidants and antidote radical free, Which can give environment physiological for process healing wound that alone.[23–26]

Gemitir flower also contains tannin 18664.28 mg/100 g TAE which is quite large. tannins act as antioxidant, agent antimicrobial, and own effect hemodynamics with narrow vessels blood And create occlusion mechanical For prevent bleeding light.[27] Content tannins speed up healing wound through a number of mechanism cellular, that is clean radical free And species oxygen reactive, improve healing wound, increase formation capillary and fibroblasts.[1]

Material experience with activity antioxidant, including extract gemitir, can increase contraction wound and speed up epithelialization, influence healing wound, Act as antioxidants And radical free, reduce peroxidation lipids, reduce cell necrotic. And increase vascularization.[27–29]. Work antioxidants Which tall from gemitir flower extract can too speed up healing wound Because stimulate production antioxidants endogenous in location wound And provide environment which good for healing wound.[30]

One of the effects of aging is the delay in the wound healing process, so treatment that accelerates wound healing is one of the steps of Anti-Aging Medicine. Gemitir flower ethanol extract has a high antioxidant effect, such as the content of flavonoids, tannins, and phenols which can accelerate the wound healing process which is proven effective in this study. Thus giving gemitir flower extract orallyisa step of Anti-Aging Medicine in preventing, inhibiting and even slowing downemergencesigns of aging and the aging process especially aging skin.

CONCLUSION

Based onthe results of this study, it can be concluded several things as follows:

(1) Giving Oral ethanol extract of gemitir flowers (*Tagetes erecta l*) increased neovascularization in wound healing in male Wistar rats (*Rattus norvegicus*) on day 4 and neovascularization decreased on day 14.
(2) Oral administration of ethanol extract of gemitir flowers (*Tagetes erecta l*) increased the number of fibroblast cells inhealingwounds of male rats (*Rattus norvegicus*) Wistar strain on day 4 and day 14
(3) Oral administration of ethanol extract of gemitir flowers (*Tagetes erecta l*) increased epithelialization in wound healing in male rats (*Rattus norvegicus*) Wistar strain on day 4 and day 14.

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