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Submission date: 13-Sep-2023 05:01PM (UTC+0800)

Submission ID: 2164899304

File name: nd-collagen-density-as-an-indicator-on-accelerating-clean-wo.pdf (278.04K)

Word count: 3313

Character count: 17256

The Effect of Topical Curcumin Extract on Fibroblast Count and Collagen Density as an Indicator on Accelerating Clean Wound Healing Process: A Study on Wistar Rats

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15

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ABSTRACT

A factor that plays an important role in the process of wound healing is fibroblast, where fibroblasts can trigger the formation of collagen. Turmeric (*Curcuma longa*) containing curcumin and volatile oil is believed to accelerate fibroblast proliferation and collagen synthesis. This study compared the effectiveness of curcumin extract topical and tulle in the acceleration the process of wound healing in rat skin. This was an experimental study using *Rattus norvegicus*. The rats were divided into four groups: group of wounds that treat with carbomer, NaCl 0.9%, tulle and curcumin extract topical, then they were compared by the fibroblast count and collagen density. In this study, there were significant differences in the number of fibroblasts among the four groups ($p = 0.034$). We found that mean fibroblast count in group of wounds treated with curcumin extract topical was higher than that treated with tulle, and we obtained $p = 0.045$. There was no difference in collagen density score between groups of wounds treated with curcumin extract topical and tulle. There was a significant difference of fibroblast count in curcumin extract topical group compared to tulle group. However, there was no significant difference in collagen density score between both of them.

Keywords: Fibroblast, collagen, curcumin extract topical, tulle, wound healing

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INTRODUCTION

Sometimes, wounds, such as punctures, sharp cuts, or surgical injuries, cannot be avoided (1). Wounds are the main cause of disability which requires a person to care of. The long duration of wound treatment will increase the cost of patient care in the hospital. The entire wound healing process involves a series of complex events that begin at the time of the injury and can continue for months to years (2). Wound healing can be influenced by many factors, both local and systemic (3-5). Recovery is one of the physiological processes after surgery. Injuries that are resolved successfully for a long time are often a problem. This incident will cause complications as a source of morbidity, because it will be psychological disturbances for sufferers, increase the budget for treatment costs, and reduce working hours for patients in productive age (6). Fibroblasts are cells that synthesize extracellular and collagen matrices, playing an important role in the process of wound healing. The number of fibroblasts reaches a peak on the 7th day after trauma and is the dominant cell in the first week of the wound healing phase [1]. Synthesis and activation of fibroblasts are performed by secretory proteins and macrophages of new extracellular matrix approvals with collagen as the structure of consent (7). Traditional wound dressing using only normal saline is relatively cheaper but has a longer shortage of wound dressing compared to modern wound dressing. In modern wound dressing, such as tulle, has synthetic polymer base material not only closes the wound but also spur the wound care (8-10).

Turmeric (*Curcuma longa*) is a rhizome plant widely known throughout the world. One of the active substances contained in turmeric is curcumin. Curcumin accelerates fibroblast proliferation and collagen synthesis and maturation (11,12).

Curcumin also contains anti-allergy and anti-bacterial activity (13,14). Hence, this study aimed to examine the comparison between turmeric extract herbal products and modern synthetic dressing tulle against the number of fibroblasts and collagen density in accelerating the healing of clean wounds on rat skin experimentally [2].

METHODS

This was an experimental study by administering topical turmeric and tulle extracts to clean rat skin wounds. The design used was a randomized posttest-only control group design. The measurement of variables was only performed at the end of the study. The sample of the study was 36 white *Rattus norvegicus* Wistar strain that met the inclusion and exclusion criteria. Criteria for inclusion of male Wistar strain white rats were age of 12-16 weeks and body weight of 250-300 grams. The exclusion criteria were during the adaptation period to behave and dressing on the wound released before the dressing replacement schedule for the next wound. The samples were divided into 4 groups based on the sample sequence number interval. The positive control was wound care using 0.9% NaCl fluid without the addition of tulle products or topical turmeric extract. Wound care was also used by adding a basic ingredient, carbomer, as a negative control variable to reduce bias. Treatment group 1 treated wound with the addition of tulle, while treatment group 2 treated wound with the addition of topical turmeric extract. The independent variable in this study was the administration of topical turmeric and tulle extracts. The dependent variables were the number of fibroblasts and collagen density assessed histopathologically. Assessment criteria was with a scoring system.

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RESULTS

In this study, the number of fibroblasts in the area was measured by wound edges on the 6th day by comparing into 4 groups. Based on the characteristics and relationships of the number of fibroblasts between the 4 groups in Table 1, the mean number of fibroblasts of the negative control group was 68.44±6.09, the positive control group was 70.00±23.08, the treatment group 1 was 71.22±24.26, and the treatment group 2 was 88.56±9.08. The number of normal and homogeneous distributed fibroblasts were examined using ANOVA statistical test, and there were significant differences in the number of fibroblasts among four groups ($p = 0.034$).

Table 1. Number of fibroblasts

Groups	Mean±SD	Min-Max	p
Negative control (N=9)	68.44±6.09	58-78	0.034*
Positive control (N=9)	70.00±23.08	44-101	
Treatment 1 (N=9)	71.22±24.26	30-103	
Treatment 2 (N=9)	88.56±9.08	72-102	

*) Anova Test

Table 2 presents the difference of the number of fibroblasts among four groups. The treatment group 2 had the highest number of fibroblasts and was statistically significant compared to the other groups ($p = 0.021$ compared to the negative control group, $p = 0.033$ compared to the positive control group, and $p = 0.045$ compared to treatment group 1).

Table 2. The difference of the number of fibroblasts

Groups		Mean Difference	p
Control Negative	Control Positive	-1.555	0.853
	Treatment 1	-2.777	0.740
	Treatment 2	-20.11	0.021
Control Positive	Negative control	1,555	0.853
	Treatment 1	-1.222	0.884
	Treatment 2	-18.555	0.033
Treatment 1	Negative control	2.777	0.740
	Treatment 1	1.222	0.884
	Treatment 2	-17.333	0.045
Treatment 2	Negative control	1,555	0.853
	Treatment 1	-1.222	0.884
	Treatment 2	-18.555	0.033

Confidence Interval = 95%

In this study, an evaluation of collagen density was carried out on the 6th day by comparing into 4 groups as seen in Table 3. In the negative control group, it was found that the highest score was 3 in 5 samples (55.6%), followed by a score of 2 in 4 samples (44.4%), and no sample was found at a score of 1 (0%). Meanwhile, the positive control group found the highest score of 3 in 5 samples (55.6%), followed by a score of 2 in 4 samples (44.4%). In the treatment group 1, the highest score was 3 in 6 samples (66.7%), followed by score 2 in 3 samples (33.3%), and no sample was found in score 1 (0%). Meanwhile, the treatment group 2 was found the highest score of 3 in 6 samples (66.7%), followed by a score of 2 in 3 samples (33.3%), and no sample was found at a score of 1 (0%). In this study, the difference in collagen density test was examined using the Kruskal Wallis test. There was no significant difference in collagen density in the

four groups ($p = 0.929$).

Table 3. Collagen Density Score

Groups	Score 1	Score 2	Score 3	p
Negative Control	0 (0%)	4 (44.4%)	5 (55.6%)	0.929*
Positive Control	0 (0%)	4 (44.4%)	5 (55.6%)	
Treatment 1	0 (0%)	3 (33.3%)	6 (66.7%)	
Treatment 2	0 (0%)	3 (33.3%)	6 (66.7%)	

*) Kruskal wallis test

DISCUSSION

We found the number of fibroblasts of curcumin treatment increased more than in the other groups. There was a significant difference in the number of fibroblasts in the topical turmeric extract group compared to the other groups. The results of this study are in line with the recent study. The curcumin can increase the number of fibroblasts [3]. This is because curcumin plays a role in inhibiting the production of Tumor Necrosis Factor-alpha (TNF- α) and Interleukin-1 (IL-1) as the two main cytokines released by monocytes and macrophages, playing a role in inducing the inflammatory response. With the inhibition of production of proinflammatory cytokine, inflammatory cells, such as polymorphonuclear, will be reduced in the wound area, thus shortening the length of the inflammatory phase and accelerating the wound healing process to enter the next healing phase, namely the proliferation phase with the formation of fibroblasts [15]. Another study also showed mice given curcumin topically in excision wounds made, showing that fibroblasts formation proceeded better than wounds treated only using ordinary gauze and primary suturing [16]. Besides curcumin, there are also some plants with wound healing effect, such as aloe vera and mangosteen (*Garcinia mangostana* Linn.) [17,18].

The number of fibroblasts has a quite different deviation. This is presumably because some animals try to get interference from the behavior of other animals in a cage which can be caused by hot environmental conditions and drinking water and feed for each mouse in a cage that is not evenly distributed because one cage contains four and five mice. In treatment group 1, we applied tulle [4]. Tulle is a synthetic textile fiber which is a polyamide resin derivative with elastic characteristics, having an penetrating properties and containing lanolin. Lanolin will create a moist atmosphere by creating a semi-occlusive barrier, preventing the wound from drying out and accelerating re-epithelialization and proliferation of fibroblasts. While in treatment group 2, we used topical turmeric extracts. Turmeric extract has many active components, such as curcumin, desmethoxycurcumin and bisdesmethoxycurcumin which function as antioxidant and anti-inflammatory effects. In addition to turmeric extract, there is another main active component, essential oil. Essential oil also has antioxidant and anti-inflammatory effects to improve the wound healing process [11,19-21].

Wound healing is the body's process to repair damaged tissue to function again. In normal condition, wound can heal by itself, but how fast it is can be affected by many factors [22]. The body tries to normalize all abnormal conditions to injury by the healing process. The body responds if the integrity of the skin is damaged in the form of overlapping phases, but can be distinguished biologically. After injury, the inflammatory phase occurs aiming to eliminate non-vital tissue and prevent invasive bacterial infections. Then, there is a proliferation phase where there is a balance between the formation of scar tissue and tissue regeneration. Finally,

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