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The effect of *Temulawak* extract gel on angiogenesis and re-epithelization rate post-tooth extraction of Wistar rats

Nyoman Ayu Anggayanti ^{1,*}, Eka Pramudita Ramadhany ², Lady Millenia Natasya ³ and Magdalena Leony Chandra ³

¹ Oral and Maxillofacial Surgery Division, Department of Dentistry, Faculty of Medicine, Udayana University, Denpasar, Indonesia.

² Periodontic Division, Department of Dentistry, Faculty of Medicine, Udayana University, Denpasar, Indonesia.

³ Bachelor Program of Dentistry, Faculty of Medicine, Udayana University, Denpasar, Indonesia.

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Abstract

Introduction: Post-extraction wound healing involves angiogenesis process followed by re-epithelialization. *Temulawak* is an herbal plant containing active substances such as curcumin, tannins and flavonoids, which could stimulate the formation of growth factors and encourage fibroblast migration. Further, it would facilitate angiogenesis and increase the migration of epithelial cells to accelerate wound healing process.

Objective: to assess the effect of 5% *temulawak* extract gel on angiogenesis and the re-epithelialization rate after tooth extraction in Wistar rats.

Methods: this study used in vivo laboratory experimental methods on 30 Wistar rats, divided into control and treatment groups. Mandibular left incisor was extracted and the Wistar rats were euthanized on the 3rd, 5th, and 7th day. The mandibles of the rats were then decapitated and observed under a microscope with 400x magnification. Data analysis was performed with SPSS Software.

Results: LSD post-hoc analysis showed a significant difference between control group day-7 and treatment group day-3, as well as treatment group day-7 ($p < 0,05$). There is also a non-significant difference in epithelial gap between control group day-5 and treatment group day-3, as well as between control group day-7 and treatment group day-5 ($p > 0,05$).

Conclusion: 5% *temulawak* extract gel has a statistically significant effect on angiogenesis and the re-epithelialization rate after tooth extraction in Wistar rats.

Keywords: *Curcuma xanthorrhiza* Extract Gel; Wound Healing; Dental Extraction; Angiogenesis; Fibroblast

1. Introduction

Tooth extraction is one of the treatment options in the field of dentistry commonly performed in cases of teeth with a hopeless prognosis. According to data from the 2018 RISKESDAS (Basic Health Research), tooth extraction is the second most common treatment procedure after medication administration to address dental and oral issues, with a prevalence of 7.9% (Ministry of Health of the Republic of Indonesia, 2018). Tooth extraction results in a wound that is subsequently followed by the wound healing process.

* Corresponding author: Nyoman Ayu Anggayanti; Email: ayu.anggayanti@unud.ac.id

The wound healing process consists of several phases, beginning with the inflammation phase, followed by the proliferation and remodeling phases. (Hupp, Tucker, and Ellis, 2019; Primadina, Basori, and Perdanakusuma, 2019). The most essential phase in the wound healing process is the proliferation phase, during which granulation tissue composed of fibroblasts and angiogenesis forms, along with the re-epithelialization process (Giridhar, 2016; Periyah MH, Halim AS, and Saad AZM, 2017).

During wound healing, the process of angiogenesis is necessary, which involves the formation of new capillaries within the wound. This process serves to maintain blood flow to the tissues after an injury, providing oxygen and nutrients to support tissue proliferation (Hupp, Tucker, and Ellis, 2019; Primadina, Basori, and Perdanakusuma, 2019). On the other hand, re-epithelialization is the process of damaged epithelial cells returning to the epidermal layer to cover the wound. The inflammatory phase during the wound healing process influences re-epithelialization (Movaffagh et al., 2022). Accelerated re-epithelialization also contributes to quicker restoration of the normal epithelial tissue structure (Rousselle, Braye, and Dayan, 2019; Waasdorp et al., 2021). Generally, socket wounds post-extraction will close within 14 days, but in immunocompromised individuals or those with specific systemic conditions, post-extraction wound healing can take longer, affecting daily activities' comfort (Balaji and Balaji, 2018; Hupp, Tucker, and Ellis, 2019).

In recent times, people have begun using herbal plants as alternatives to chemical medications to aid and expedite the wound healing process. One widely used plant is *temulawak* (*Curcuma xanthorrhiza roxb.*). The compound curcumin in *temulawak* acts as an antimicrobial and anti-inflammatory agent that can accelerate the inflammatory phase and enhance fibroblast production, thus promoting epithelial cell migration. *Temulawak* contains flavonoids and tannins with astringent properties that cause wound contraction, reducing the surface area that needs to be covered by epithelial cells. These flavonoids can stimulate the formation of new epithelial cells and angiogenesis, speeding up the re-epithelialization process (Palumpun, Wiraguna, and Pangkahila, 2017; Kristianto, 2021; Heri et al., 2022). The abundance of bioactive substances in *temulawak* supports its significant potential for accelerating wound healing, providing greater comfort to patients, especially after tooth extraction. However, research regarding the use of *temulawak* extract gel in the post-tooth extraction wound healing process is still limited. This study aims to assess the effects of 5% *temulawak* extract gel on angiogenesis and re-epithelialization rate after tooth extraction in Wistar rats.

2. Methods

The tools and materials used in this study include *Temulawak* (*Curcuma xanthorrhiza roxb.*), CMC-Na (Sodium Carboxymethyl Cellulose), 96% ethanol, blender, knife, stirring rod, oven, tray, evaporating flask, rotary evaporator, Büchner funnel, glass funnel, measuring glass, Erlenmeyer flask, analytical balance, 40 mesh sieve, Whatman filter paper, Wistar strain rats, cages and lids, rat food, wood powder, deionized water, anesthesia (ketamine hydrochloride & xylazine hydrochloride), hemostat, cannula, 1 cc syringe, surgical scissors, needle holder, Hematoxylin Eosin (HE) staining equipment, glass coverslip, microscope slides, 10% formalin buffer solution, xylene solution, HE solution, paraffin, alcohol (70%, 80%, 90%, 95%, and 100%), tissue pots, digital microscope, hand gloves, and surgical masks.

The research design used is in vivo laboratory experimentation on Wistar rats with a post-test only control group research design. The method used to select samples is random sampling, where the samples are then divided into 2 groups: the treatment group (given 5% *temulawak* extract gel in post-tooth extraction socket) and the control group (given placebo gel). This research took place in the Phytochemistry Laboratory of the Faculty of Mathematics and Natural Sciences, Udayana University, and the Laboratory of the Faculty of Veterinary Medicine, Udayana University. This study has been approved by the ethics and ethics committee of the Faculty of Medicine, Udayana University. The minimum sample size calculated using the Federer formula is 30 rats, with an additional 10% to account for potential data incompleteness (dropouts).

2.1. The process of making *temulawak* extract gel

The process of making *temulawak* extract gel begins with peeling and thoroughly washing the *temulawak* rhizomes under running water. Afterward, they are cut into small pieces and dried using an oven. Once dried, the *temulawak* is ground into a powder using a blender. The subsequent step is the maceration process, involving dissolving 1000 grams of *temulawak* powder in 2 liters of 96% ethanol solution. This mixture is stirred for 10 minutes and left to rest for 24 hours. After this, the solution is filtered using a Büchner funnel lined with filter paper. The obtained residue undergoes maceration again, this time with another 2 liters of 96% ethanol, and is left to rest for another 24 hours. The solution is then filtered again, and the collected filtrates are combined and evaporated using a water bath until a concentrated extract is formed. Subsequently, the extract is left to air-dry, separating the oil from the extract. The extract is then transferred to a container for further processing into a gel preparation. The initial step in making the *temulawak* extract gel involves the preparation of CMC-Na (Sodium Carboxymethyl Cellulose). 4 grams of CMC-Na is dispersed in hot water

and stirred until it becomes homogeneous. Then, the *temulawak* extract is gradually added and stirred until homogenous. The resulting *temulawak* extract gel is then transferred to containers.

2.2. Extraction of the mandibular incisors teeth in Wistar rats

The previous research samples were acclimated at the Udayana University Veterinary Hospital for 7 days. During this period, they were provided with pellet food and water (aquades). The animals were housed in cages with bedding made of sawdust. On the treatment day, the experimental animals were anesthetized through intramuscular injection with a mixture of 75 mg/kg body weight of ketamine and 5 mg/kg body weight of xylazine. The left mandibular incisor was luxated using a needle holder.

2.3. Application of 5% *temulawak* extract gel

Application of 5% *temulawak* extract gel in the treatment group is performed topically, applying 0.1 ml using a syringe and cannula to the post-tooth extraction socket. The gel is applied twice a day in the morning (10:00 AM) and in the afternoon (4:00 PM).

2.4. Preparation and observation of histological slides

Euthanasia of the experimental animals is conducted on days 3, 5, and 7 by administering an overdose of ketamine at a dosage of 60-75 mg/kg through intraperitoneal injection. Before euthanasia, ensure that the Wistar rats are unconscious. Anesthesia is induced using a combination of ketamine and xylazine. Subsequently, the decapitation of the mandible is performed, and the mandibles of the Wistar rats are stored in closed plastic containers containing 10% formalin buffer solution. The experimental animals' cadavers are then properly buried. Following this, the process of creating histological slides and staining with Hematoxylin Eosin is initiated. The calculation and observation of blood vessels (angiogenesis) are carried out using a light microscope and an Optilab digital camera with a magnification of 400x in three fields of view. The observed blood vessels appear as rounded or elongated lumens bounded by cell walls and surrounded by endothelial cells, with or without red blood cells inside. The thickness of the epithelium is measured by summing the maximum and minimum thickness and dividing by two (in micrometers). Epithelial width is measured from one end of the epithelium to the opposite end facing it. A smaller value and distance between epithelial gaps indicate a more effective re-epithelialization process.

2.5. Data analysis

The data and research results were quantitatively processed using the SPSS application. Normality testing was conducted using the Shapiro-Wilk test since the sample size was less than 50. Data is considered normally distributed if the significance value is > 0.05 . If the data is normally distributed, the Levene's test for homogeneity is performed to determine whether two or more data groups have the same variance ($p > 0.05$) or not. Parametric hypothesis testing is conducted for normally distributed and homogenous data using One-Way ANOVA with a confidence level of 95% (p

> 0.05). This is followed by post hoc testing, such as the Least Significant Difference (LSD) test, to identify significant differences. If the results show that the data is not normally distributed and not homogenous, non-parametric hypothesis testing is conducted using the Kruskal-Wallis test with a confidence level of 95% ($p > 0.05$). This is followed by post hoc testing, such as the Mann-Whitney test.

3. Results

The results of the histological slide observations were then recorded and analyzed using the SPSS application. Data normality was tested using the Shapiro-Wilk test, and homogeneity was tested using Levene's test. The testing results with data $p > 0.05$ indicated that the data was normally distributed and homogenous. Consequently, a parametric test, One-Way ANOVA, was performed. The One-Way ANOVA results indicated that the data from the control group and treatment group with decapitation days 3, 5, and 7 had significant differences in angiogenesis counts ($p < 0.05$). The data analysis was then continued with a post-hoc LSD test.

The LSD test results showed significant mean differences in angiogenesis counts between K3 and K5, K7, P3, P5, and P7 ($p > 0.05$) (Table 1). There were significant mean differences in angiogenesis counts between K5 and K7, P5, and P7 ($p > 0.05$). There was a significant mean difference in angiogenesis counts ($p > 0.05$) between K7 and P3, as well as K7 and P7. There were no significant mean differences in angiogenesis counts between K5 and P3, and K7 and P5.

A Mann-Whitney test was also conducted to assess the epithelial thickness for evaluating the rate of re-epithelialization, as shown in Table 2. The Mann-Whitney test results indicated significant mean differences in epithelial thickness

between K3 and K5, K7, P3, P5, and P7 ($p < 0.05$). There were significant differences in epithelial thickness between K5 and K7, P5, and P7 (p

< 0.05). Significant mean differences ($p < 0.05$) were observed between K7 and P7. Significant mean differences ($p < 0.05$) were found between P3 and P5, as well as P3 and P7. There were significant mean differences ($p < 0.05$) between P5 and P7. However, no significant mean differences in epithelial thickness were observed between K5 and P3, K7 and P3, and K7 and P5.

Subsequently, the post-hoc LSD test results regarding epithelial gap width in the study are presented in Table 3. These results showed significant mean differences in epithelial gap width between K3 and K5, K7, P3, P5, and P7 ($p < 0.05$). There were significant differences in epithelial gap width between K5 and K7, P5, and P7 ($p < 0.05$). Significant mean differences ($p < 0.05$) were found between K7 and P3, as well as between K7 and P7. Significant mean differences ($p < 0.05$) were observed between P3 and P5, and P3 and P7. There were significant mean differences ($p < 0.05$) between P5 and P7. However, no significant mean differences in epithelial gap width were observed between K5 and P3, and K7 and P5.

Table 1 LSD Post-Hoc Test Results for Post-Extraction Socket Angiogenesis

	K3	K5	K7	P3	P5	P7
K3						
K5	0.001					
K7	0.000	0.006				
P3	0.002	0.150	0.000			
P5	0.000	0.005	0.626	0.000		
P7	0.000	0.000	0.001	0.000	0.001	

Table 2 Mann Whitney Test Results for Post-Extraction Socket Epithelial Thickness

	K1	K2	K3	P1	P2	P3
K3						
K5	0.031*					
K7	0.000*	0.000*				
P3	0.046*	1.000	0.375			
P5	0.000*	0.013*	1.000	0.009*		
P7	0.000*	0.000*	0.000*	0.000*	0.000*	

Table 3 LSD Post Hoc Test Results for Post-Extraction Socket Epithelial Gaps

	K1	K2	K3	P1	P2	P3
K1						
K2	0.002*					
K3	0.000*	0.036*				
P1	0.003*	0.856	0.025*			
P2	0.000*	0.001*	0.101	0.001*		
P3	0.000*	0.000*	0.000*	0.000*	0.000*	

Information: K1: Control Group Decapitation on Day 3 K2: Control Group Decapitation on Day 5 K3: Control Group Decapitation on Day 7 P1: Treatment Group Decapitation on Day 3 P2: Treatment Group Decapitation on Day 5 P3: Treatment Group Decapitation on Day 7

The analysis results indicate a non-significant difference between the control group on day 5 and the treatment group on day 3, as well as between the control group on day 7 and the treatment group on day 5. This suggests that when the treatment is administered to the rat groups up to day 3 and 5, the number of blood vessels is almost the same compared to the control group on days 5 and 7. Therefore, it can be concluded that the 5% *temulawak* extract gel (*Curcuma xanthorrhiza roxb.*) is effective in accelerating post-tooth extraction angiogenesis in Wistar rats (*Rattus norvegicus*). The graph depicting the differences in epithelial thickness and epithelial gap between the treatment and control groups can be seen in Figure 1. The results of this study indicate that the treatment group on day 7 has the highest average number of blood vessels, which is 141.25 blood vessels. The difference in mean blood vessel count between the control and treatment groups on day 7 is 23.75 blood vessels.

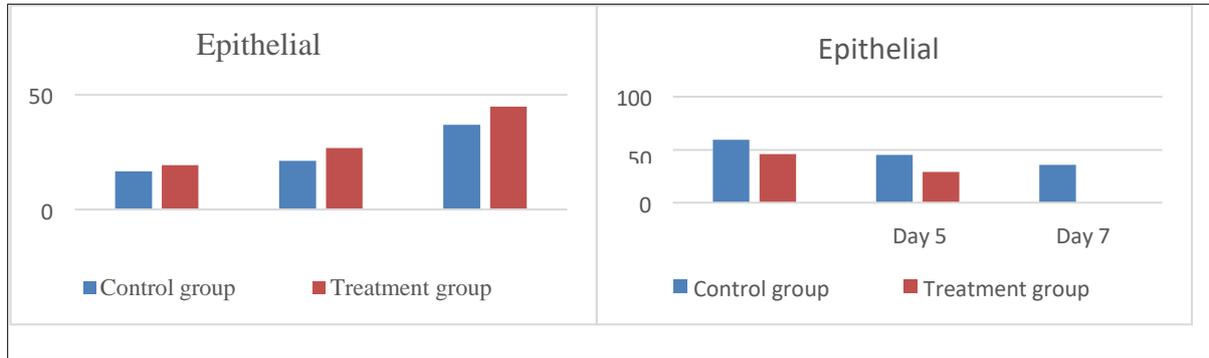


Figure 1 Graph depicting the differences in epithelial thickness and epithelial gap between the control group and the treatment group.

4. Discussion

Based on the research results, the treatment group exhibited higher levels of angiogenesis, epithelial thickness, and epithelial gap compared to the control group in observations on days 3, 5, and 7. Similar findings were demonstrated by Li et al. (2021), who showed faster wound healing and fibroblast formation in the sockets of male Wistar rats with periodontitis treated with Curcumin extract gel. This effect can be attributed to the stimulating and anti-inflammatory capabilities of the bioactive compounds present in herbal plant extracts.

Based on phytochemical testing, *temulawak* contains active compounds such as flavonoids, alkaloids, tannins, saponins, phenols, terpenoids, and curcuminoids (Li et al., 2021). The main component in *temulawak* is curcuminoid, found exclusively in the rhizomes of *temulawak*. Previous studies have shown that curcuminoids in *temulawak* have been proven to significantly enhance wound healing by increasing collagen deposition, accelerating angiogenesis, and fibroblast density (Asiyah, 2018; Kesumayadi et al., 2021; Li et al., 2021). Curcuminoids can stimulate growth factors such as TGF- β , which play a role in early granulation tissue formation during wound healing. TGF-

β also stimulates the formation of new blood vessels, thereby expediting the wound healing process (Heri et al., 2022). Curcuminoids possess anti-inflammatory activity by inhibiting COX-2 and LOX enzymes, which are significant during the inflammation phase. Curcuminoids also act as anticoagulants, preventing thrombosis under certain conditions, and function as antioxidants, aiding wound healing by controlling oxidative stress (Asiyah, 2018; Li et al., 2021).

Flavonoids present in *temulawak* also play a role in regulating cellular functions by stimulating the production of TGF- β and inducing VEGF, both of which are involved in the formation of new blood vessels (Busman et al., 2020; Li et al., 2021). Additionally, flavonoids can enhance epithelial cell proliferation and the formation of granulation tissue. This effect is achieved by increasing collagen production and angiogenesis at the wound site. Flavonoids are known to increase IL-2 levels and lymphocyte proliferation, which subsequently influence the formation of CD4+ cells and activate Th1 cells. The activation of Th1 cells enhances the growth factors that contribute to angiogenesis, fibroplasia, and re-epithelialization. Flavonoids also stimulate HIF-1, which induces VEGF, thus accelerating the formation of new blood vessels. Another component with a role in the wound healing process is tannin, which can expedite wound healing by increasing fibroblast proliferation, angiogenesis, and wound contraction (Tripathi et al., 2019; Carvalho et al., 2021; Lu et al., 2022). Saponins, also identified in *temulawak*, stimulate angiogenesis by boosting VEGF formation, a critical mediator in the creation of new blood vessels. VEGF enhances the activity of protease enzymes that function in the degradation of the extracellular matrix for the branching of new blood vessels (Irham and Marpaung, 2019).

In this study, *temulawak* extract was formulated into a gel using the gelling agent CMC-Na. This choice was made because the resulting gel viscosity would be more stable, and the gel would remain neutral. Gels were chosen due to their good drug release capabilities and their ability to maintain wound moisture (Obagi et al., 2019; Weller and Team, 2019; Nuutila and Eriksson, 2021). A moist wound environment stimulates the formation of growth factors such as VEGF, FGF-2, angiopoietin-1, and thrombospondin, which in turn stimulate the formation of new blood vessels (Tan and Dosan, 2019; Primadani and Safitri, 2021). The research conducted demonstrates that the application of *temulawak* extract gel to the socket wound of Wistar rats effectively accelerates the re-epithelialization process. This is also evidenced by the narrowing of the epithelial gap formed. The faster the re-epithelialization process, the quicker the wound closure, leading to an expedited wound healing process. One sign of a successful re-epithelialization process is the absence of an epithelial gap or complete closure of the epithelial gap (Primadina, Basori, and Perdanakusuma, 2019; Kamal et al., 2021; Heri et al., 2022).

5. Conclusion

A 5% *temulawak* extract gel (*Curcuma xanthorrhiza roxb.*) can accelerate the process of angiogenesis and re-epithelialization after tooth extraction in Wistar rats (*Rattus novergicus*).

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

This animal study received ethical approval from the Ethical Committee at the Faculty of Medicine, Udayana University (No.311/UN114.2.2.VII.14/LT/2021). All research procedures were conducted in strict accordance with ethical guidelines and relevant regulations.

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