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Original article

Effects of 3% Mobe (*Artocarpus lakoocha*) leaf extract gel on the post-extraction socket: In-vivo study

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ABSTRACT

Background: *Mobe (Artocarpus lakoocha) is recognized for its potential in accelerating wound healing, attributed to its secondary metabolites. However, its impact on hard tissue healing on post- extraction tooth sockets has been underexplored.* ***Purpose:*** *This study aims to analyze the effects of 3% Mobe leaf extract gel on the number of fibroblasts, osteoblasts, osteocytes and post-extraction sockets in Wistar rats.* ***Methods:*** *Thirty-two male Wistar rats had their left mandibular incisors extracted and were divided into eight groups. Mobe leaf extract gel was applied to Group I-IV and Aloclair® gel was applied to Group V-VIII for 14 days, twice a day. Residual socket volume (RSV) and fibroblast counts were measured on days 3, 7, and 14, while osteoblast and osteocyte counts were assessed on days 7, 14, and 28 post extraction. The RSV data were analyzed using repeated measures analysis of variance (ANOVA) and post-hoc least significant difference (LSD) test, while fibroblasts, osteoblasts, and osteocytes counts were analyzed with one-way ANOVA and post-hoc LSD tests.* ***Results:*** *RSV decreased significantly in both groups on day 14 (p=0.001 and p=0.002); however, the RSV was lower on the Mobe group. The fibroblast counts were higher in the Mobe group (p=0.001), and there was a significant difference in the mean number of osteoblasts and osteocytes in the Mobe group (p= 0.043 and p=0.008).* ***Conclusion:*** *The study concludes that 3% Mobe leaf gel extract is better than Aloclair® in accelerating socket healing mainly due to increased proliferation of fibroblasts, osteoblasts, and osteocytes.*

Keywords: *Artocarpus lakoocha; fibroblasts; osteoblasts; osteocytes; wound healing*
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INTRODUCTION

One of the most commonly performed dental procedures is tooth extraction. In Indonesia, there are approximately 44,000 tooth extraction cases every year.[1] Tooth extraction leaves a socket wound. Generally, wound healing in post-extraction sockets is similar to wound healing in soft tissues. This process consists of the inflammatory phase, proliferative phase, and remodeling phase.[2] However, the healing of hard tissue is also involved in tooth socket healing.[3] After tooth extraction, wound healing process in the alveolar bone is a highly coordinated process of bone formation and also involves communication between different types of cells present in the bone tissue, such as osteoblasts, osteocytes, and fibroblasts, among others.[4]

Fibroblasts play a role in the final phase of inflammation and the initial phase of proliferation, while the main cells play a major role in the remodeling phase.[5–7] Fibroblast formation begins on the third day and reaches its peak on the seventh day after the injury.[8] Fibroblasts are responsible for the production of most of the extracellular matrix in the connective tissue and are important for wound healing and repair.[9,10] At the beginning of the formation of hard tissue, the cells that play an important role are fibroblast cells, because these cells synthesize elastic connective tissue fibers, proteoglycans, glycosaminoglycans, reticular, and adhesive glycoproteins that contribute to the formation of granulation tissue, which has a very large number of blood vessels. This purposes to improve tissue integrity and lays the groundwork for bone formation, orchestrated

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by the three main bone-forming cells, namely osteoblasts, osteoclasts, and osteocytes in the remodeling phase.[11,12]

Osteoblasts have a role in the proliferative as well as remodeling phase of new bone formation.[13] Osteoblasts began to form and differentiate on the seventh day after tooth extraction and reached their peak on day 14, while the maturation of osteoblasts into osteocytes proceeded until day 28 post tooth extraction.[8] Osteocytes are matured osteoblasts trapped in the bone matrix and play a role during the remodeling phase by regulating the activity of osteoblasts and osteoclasts.[5] Osteocytes began to be seen in the trabecular bone on day 28 after tooth extraction.[6]

Effective wound closure is produced through the formation of granulation tissue and control of wound contraction, followed by the return of tissue integrity to what it was before the wound.[7] The wound begins to contract about seven days after its occurrence, mainly mediated by myofibroblasts, resulting in a smaller wound.[14] The fibroblast level activity after wound closure decreases to normal levels around the 14th day, when the new extracellular matrix (ECM) in the wound has the same tensile strength as the surrounding healthy tissue.[7,8]

In tooth extraction procedures, it is highly possible for various complications to occur, such as bleeding, dry socket, and edema, which can slow down the wound healing process.[15] The use of drugs (Aloclair® gel) is known to speed up the wound healing process; however, chemical drugs are known to have side effects, such as causing allergic reactions.[16] Therefore, other alternatives are needed from herbal ingredients, which have minimal side effects and are low in cost.

Mobe (*Artocarpus lakoocha*) is a plant that has been widely used by the community as an alternative treatment. In Thailand, this plant is used to heal wounds and prevent premature aging.[17] Mobe plant contains artocarpine, a compound known for its significant role in the wound healing process. Artocarpine stimulates neutrophil migration, promotes collagen deposition, enhances re-epithelialization, and facilitates the formation of new blood vessels. These mechanisms collectively contribute to the efficient and effective healing of wounds. In addition, during the remodeling phase, artocarpine can also stimulate myofibroblast levels and wound contraction by increasing transforming growth factor beta (TGF-β).[18] Applying Mobe leaf ethanol extract ointment with a concentration of 5% can reduce the wound diameter, resulting in quick wound healing.[17] Another study showed that giving 3% Mobe leaf extract gel had the best effect in accelerating wound closure both clinically and microscopically.[19]

Based on this understanding, Mobe leaf holds considerable promise as a medicinal plant. However, the specific impact of Mobe leaf extract gel on the hard tissue healing process remains unclear. Therefore, the objective of this study is to investigate the impact of 3% Mobe leaf extract gel on wound closure and the proliferation of fibroblasts, osteoblasts, and osteocytes on alveolar wound healing in Wistar rats after tooth extraction.

MATERIALS AND METHODS

The study obtained approval from the Ethics Committee for Animal Use at the Faculty of Mathematics and Natural Science, Universitas Sumatera Utara, Medan (0200/KEPH-FMIPA/2021 and 0205/KEPH-FMIPA/2021). This research was an in-vivo experiment with a post-test only control group design. The Mobe leaf extract utilized in the study was sourced from the Pharmacognosy Laboratory, Faculty of Pharmacy, Universitas Sumatera Utara, Medan, North Sumatra, Indonesia.

A total of 400 g of Mobe leaves was taken; the selected Mobe leaves were approximately 12 weeks old, fully-opened, and cultivation was carried out without the use of pesticides and obtained from the Laguboti District, Toba Samosir, North Sumatra Province, Indonesia. First, the Mobe leaves were washed in running water; then, the leaves were dried and weighed (Pocket Scale MH-Series). After that, the leaves underwent a process of maceration using a mixer until they reached a powdery consistency, were immersed in 80% ethanol within a sealed container, and left to distill for five days at room temperature. Subsequently, the 80% ethanol solvent was exchanged with fresh solvent, allowed to soak for an additional two days, and then filtered. The filtered powder was evaporated with a water bath until the extract was dried out.[20]

In the first mixture, 0.125 g of carbopol, 1.5 g of *triethanolamine* (TEA), and 2 g of glycerin were stirred together with 10 mL distilled water in a clockwise motion until the mixture was homogeneous. In the second mixture, 0.125 g *hydroxypropyl methylcellulose* (HPMC), 0.02 g nipagin, and 0.02 g nipasol were stirred together with distilled water in a clockwise motion until the mixture was homogeneous. The two mixtures were combined together until they became homogeneous. To ensure the freshness of each batch, only 20 g of 3% Mobe leaf extract gel was made at a time, 3% extract is 3/100 x 20 g, which meant 0.6 g of Mobe leaf extract was added and dissolved in the mixture until it was homogenous (Figure 1).

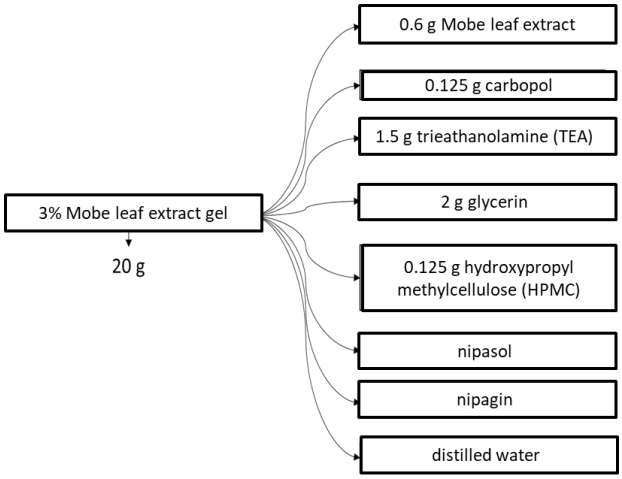

Figure 1. The composition of 3% Mobe leaf extract gel.

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Before the experimental procedure, all the Wistar rats (*Rattus novergicus*) used in this study were acclimatized for a week to allow adaptation to their new environment. The sample size for the study, which reported an effect size (Cohen's D) of 3.31 between the experimental and control groups, was determined based on prior studies of similar nature.[3] After calculation, the minimal sample size required was three animals, which was adjusted to four animals per group (totaling eight groups) or 32 animals overall. The minimum sample size was increased by 10% to prevent samples from being excluded during the experiment. The rats in the study were male rats, aged 2-3 months old, and weighing between 200-250 g; they had never been treated before. Rats displaying anomalies or those that died before the conclusion of the experiment were eliminated from the study. The rats were divided into eight groups, namely the experimental groups, which were given 3% Mobe leaf extract gel (group I, II, III, and IV) and the positive control groups, which were given Aloclair® gel (group V, VI, VII, and VIII) (Figure 2). Each group consisted of four samples.

The residual socket volume (RSV) and fibroblast proliferation were examined on the days 3, 7, and 14 post extraction, since generally, the wounds healed completely and closed by the 14th day, while the osteoblast and osteocyte proliferation were examined on days 7, 14, and 28 post extraction. A combination of ketamine and xylazine at a dose of 0.1 ml/100 g of rat weight was used intraperitoneally (i.p.) to anesthetize the rats. Artery clamp (Caredent, UK) was used to extract the left mandibular incisor of the rats with a luxation motion until the tooth was extracted completely. The post-extraction socket was cleaned of the remnants of blood and debris with distilled water.[21] Then, the initial measurement of the socket volume was carried out using a pair of compasses (Joyko®, Indonesia), a caliper (Digital Caliper, China), and a periodontal probe (Kohler 3182, Germany) to measure the mesial-distal width, buccal-lingual width, and probing depth. For each socket, 0.1 ml of gel application was carried out using a 1 ml syringe (One Med Health Care, 2019, PT. Jayamas Medica Industri) with a bent needle irrigation tip (Ivoclar Vivadent; Ø: 1.2 mm) until the entire surface of the socket was covered with gel. Gel application was done twice a day between 08.00-10.00 a.m. and 4.00-6.00 p.m. for 14 days.

To avoid bias, the measurements of residual socket volume were performed on group III and VII rats, which were observed until the 14th day, enabling repeated measurements on the same samples.[22] These measurements were conducted blindfolded by the same researcher. The average socket volume for each Wistar rat was computed. The residual socket volume measurements for each rat were obtained on days 3, 7, and 14 and then divided by the volume of the socket on day 1 (the volume measured directly after extraction) to compare socket closure in the Mobe leaf extract gel group and the Aloclair group®. Socket volume (in mm^3) can be calculated by the formula:[23]

Socket volume = mesial-distal width x buccal-lingual width x probing depth

Measurements were carried out three times, and the average measurements were taken for each rat. The rats were humanely euthanized by neck dislocation. Subsequently, the rat's jaw was excised, and the alveolar bone tissue was carefully removed from the socket. Buffered Neutral Formalin (BNF) 10% solution was used to fix the tissue for 1-2 days, followed by decalcification of the tissue by immersing it in 10% EDTA solution for ten days.[24] Tissue processing was performed by staining with Masson's Trichrome to see fibroblast cells, and Hematoxylin Eosin staining was done to see osteoblasts and osteocytes microscopically (Primo Star, Carl Zeiss).[25] The number of fibroblasts, osteoblasts, and osteocytes were calculated using the mean cell count observed using a microscope with 400X magnification in ten fields of view. Using a tally counter and calculator (Alfalink), fibroblasts, osteoblasts, and osteocytes were counted twice in each field of view by two observers. Then, all the results obtained were averaged.[26] Repeated measures analysis of variance (ANOVA) was used to analyze the RSV while one-way ANOVA was used to analyze the fibroblasts, osteoblasts, and osteocytes proliferations. Multiple comparisons were performed by least significant difference (LSD). A P-value below 0.05 was deemed as statistically significant.

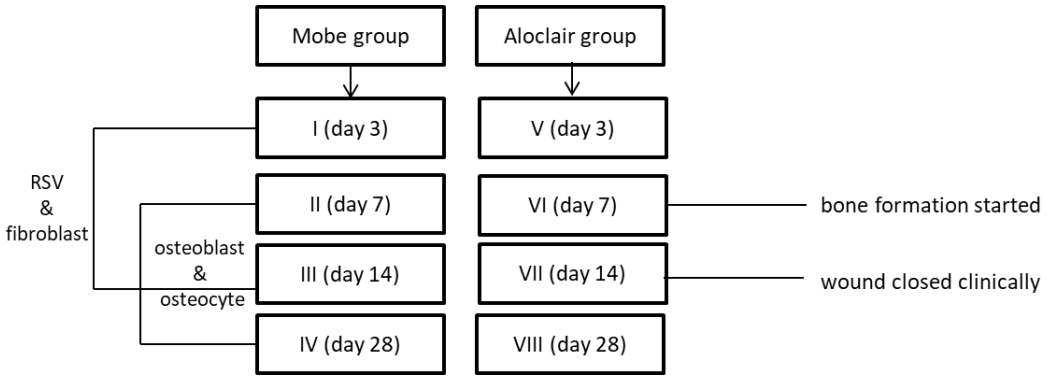

Figure 2. Experimental groups and positive control groups.

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RESULTS

Figure 3A shows that the RSV value of both groups decreased over time, indicating that the socket wound was reducing in size. Repeated measures ANOVA revealed significant differences (p = 0.001 and p = 0.002) in RSV values between the 3% Mobe leaf extract gel group and the Aloclair® gel group. Smaller RSV values were obtained in the gel group with Mobe leaf extract, so it can be assumed that the wound closure in the 3% Mobe leaf extract gel group was better than that of the Aloclair® group (Figure 4). Post-hoc LSD test results (Table 1) revealed a significant difference in residual socket volume (RSV) values within the 3% Mobe leaf extract gel group between days 3 and 7, days 3 and 14, and days 7 and 14 (p = 0.040, p = 0.005, and p = 0.001).

Figures 3B and 5 show that the mean cell counts of fibroblasts in both groups peaked on day 7 post extraction and subsequently declined on day 14 post extraction. One-way ANOVA test showed significant differences in the 3% Mobe leaf extract gel group and the Aloclair® group (p=0.001 and p=0.001). Post-hoc LSD test results (Table 2) revealed that the 3% Mobe leaf extract gel group had a significant difference in fibroblasts between days 3 and 7, days 3 and 14, and days 7 and 14 (p = 0.001, p = 0.011 and p = 0.001).

Figures 6A and 7 show that osteoblasts increased from day 7 to 14 and decreased from day 14 to 28. This might be because osteoblasts began to appear on the 7th day after tooth extraction, with peak differentiation and proliferation of osteoblasts observed on the 14th day post extraction, leading to an increase in osteoblast numbers. A one-way ANOVA test showed a significant difference (p = 0.043) in 3% Mobe leaf extract gel group. Post-hoc LSD test results (Table 3) revealed a significant difference in osteoblast counts between day 7 and 14 (p = 0.015).

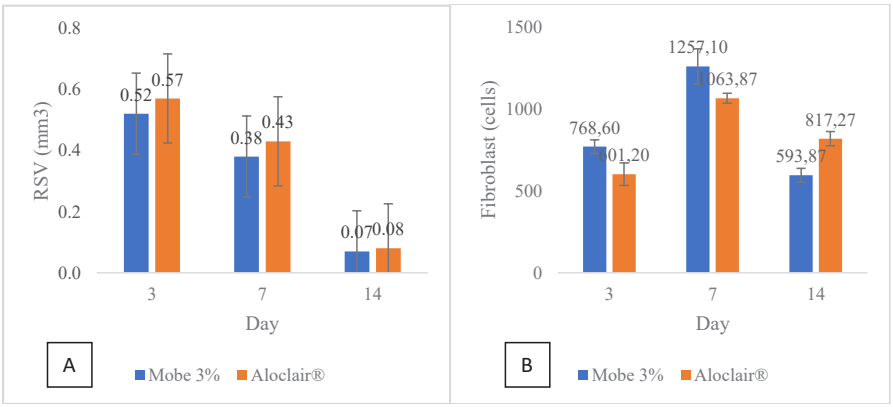

Figure 3. Diagram of residual socket volume (RSV) (A) and mean number of fibroblasts (B) in the 3% Mobe leaf extract gel group and Aloclair® gel group on days 3, 7, and 14.

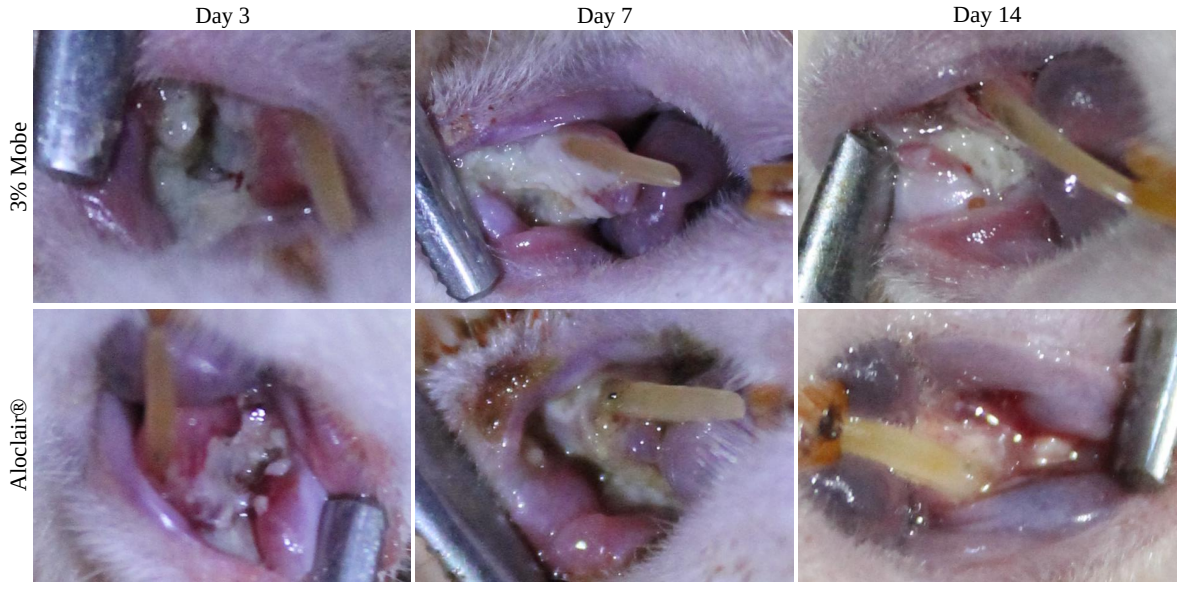

Figure 4. Wound closure on days 3, 7, and 14 in the 3% Mobe leaf extract gel group and Aloclair® gel group after tooth extraction of male Wistar rats.

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However, no significant differences were observed between day 7 and 28 or between day 14 and 28 (p = 0.209 and p = 0.106).

Figures 6B and 7 show that the mean number of osteocytes increased from day 7 to 28 in both groups. The one-way ANOVA test revealed a significant difference (p = 0.008) in the 3% Mobe leaf extract gel group. Post-hoc LSD test results (Table 4) indicated significant differences (p = 0.010 and p = 0.004) in the 3% Mobe leaf extract gel group between day 7 and 14 as well as between day 7 and 28. However, there was no significant difference (p = 0.735) observed between day 14 and 28.

Table 1. LSD post-hoc test results mean RSV on days 3, 7, and 14 after tooth extraction of male Wistar rats

Group	Observation		**p-values**
Mobe 3%	Day 3	Day 7	0.040*
		Day 14	0.005*
	Day 7	Day 14	0.001*
Aloclair®	Day 3	Day 7	0.074
		Day 14	0.023*
	Day 7	Day 14	0.010*

* LSD *post-hoc*; p<0.05; significant

Table 2. LSD post-hoc test results number of fibroblasts on days 3, 7, and 14 after tooth extraction of male Wistar rats

Group	Observation		**p-values**
Mobe 3%	Day 3	Day 7	0.001*
		Day 14	0.011*
	Day 7	Day 14	0.001*
Aloclair®	Day 3	Day 7	0.001*
		Day 14	0.002*
	Day 7	Day 14	0.001*

* LSD *post-hoc*; p<0.05; significant

Table 3. LSD post-hoc test results number of osteoblasts on days 7, 14, and 28 after tooth extraction of male Wistar rats

Group	Observation		p-values
Mobe 3%	Day 7	Day 14	0.015*
		Day 28	0.209
	Day 14	Day 28	0.106
Aloclair®	Day 7	Day 14	0.436
		Day 28	0.460
	Day 14	Day 28	0.967

* *Post-hoc* LSD; p<0.05; significant

Table 4. LSD post-hoc test results number of osteocytes on days 7, 14, and 28 after tooth extraction of male Wistar rats

Group	Observation		p-values
Mobe 3%	Day 7	Day 14	0.010*
		Day 28	0.004*
	Day 14	Day 28	0.735
Aloclair®	Day 7	Day 14	0.262
		Day 28	0.144
	Day 14	Day 28	0.674

**Post-hoc* LSD; p<0.05; significant

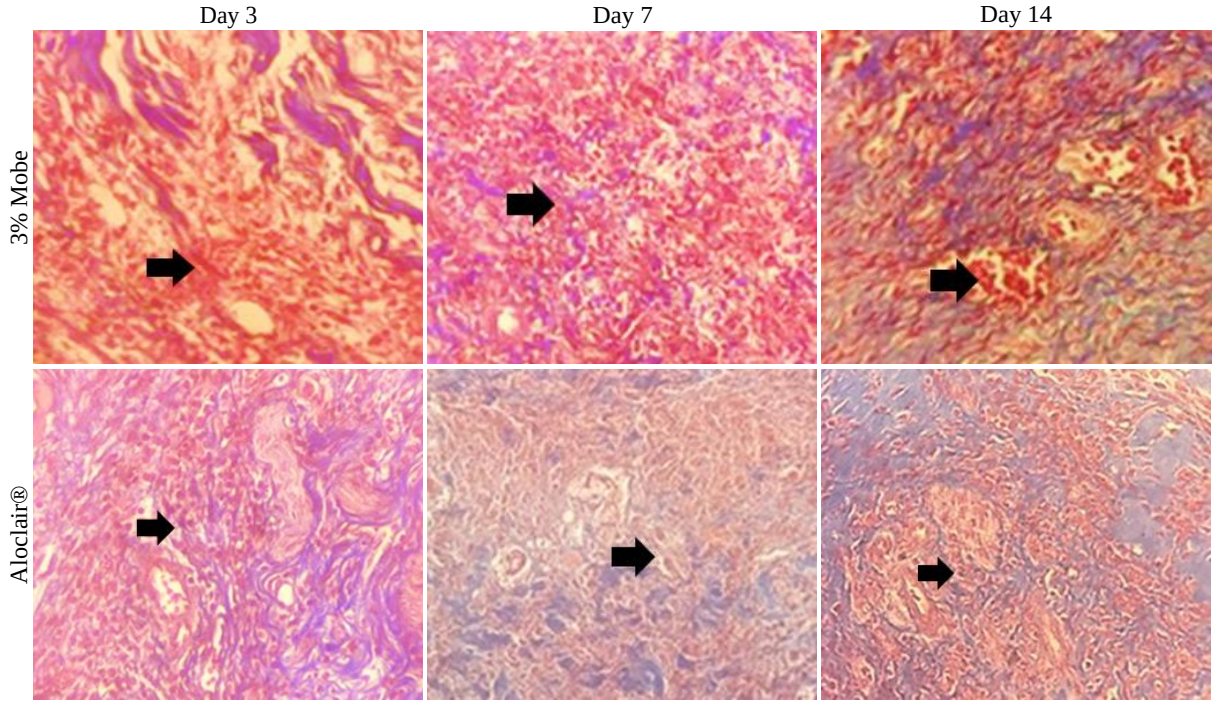

Figure 5. Histological observations of fibroblasts (black arrows) after tooth extraction of male Wistar rats in the 3% Mobe leaf extract gel group and Aloclair® gel group on days 3, 7, and 14 stained with Masson's trichrome.

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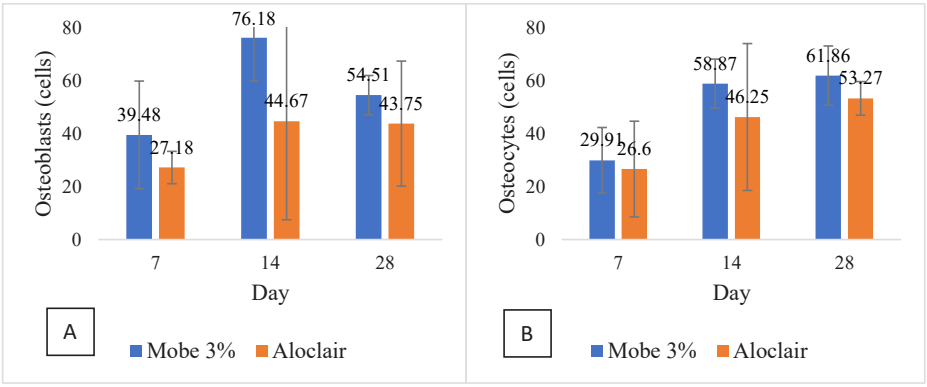

Figure 6. Diagram of the mean number of osteoblasts (A) and osteocytes (B) in the 3% Mobe leaf extract gel group and Aloclair® gel group on days 7, 14, and 28.

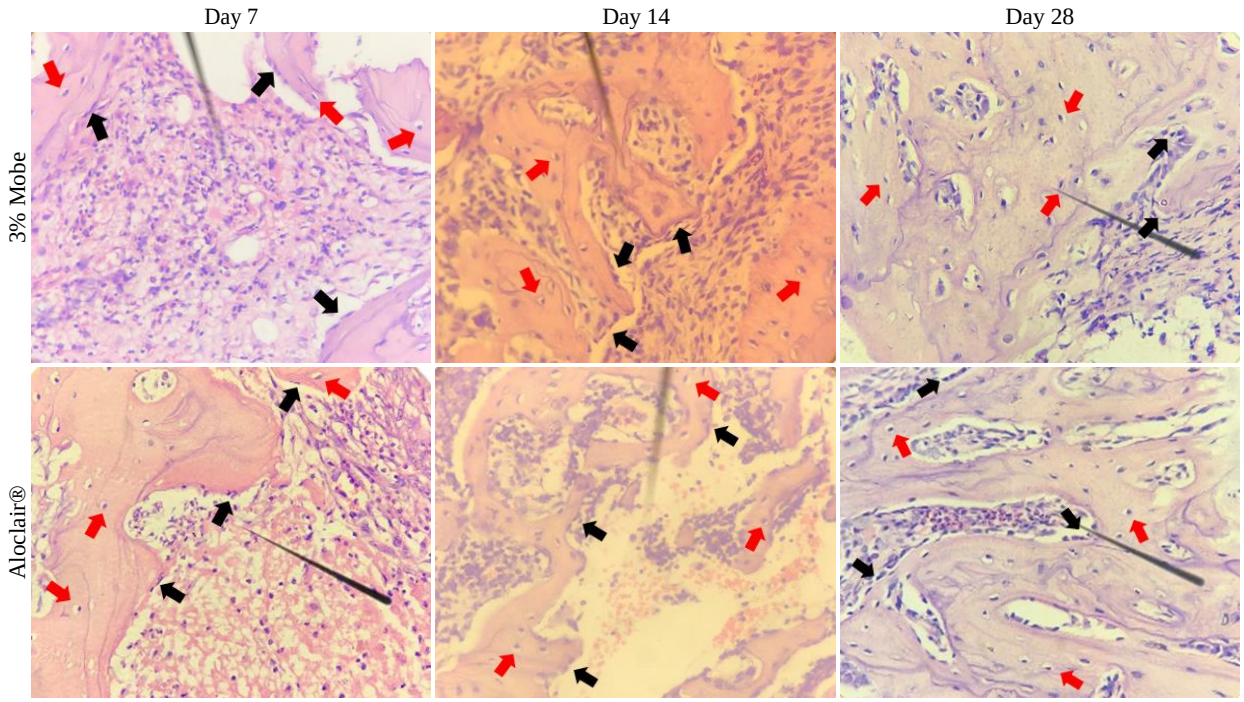

Figure 7. Histological observations of osteoblasts (black arrows) and osteocytes (red arrows) after tooth extraction of male Wistar rats in the 3% Mobe leaf extract gel group and Aloclair® gel group on days 7, 14, and 28 stained with Hematoxylin Eosin.

DISCUSSION

After tooth extraction, the wound healing process in the socket involves repair of both soft and hard tissues.[27] In the inflammatory phase, a hematoma forms in the tooth socket area and then, platelets attach to the damaged blood vessel wall and activate cytokines and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β1 (TGF-β1), thromboxane A-2, and serotonin, thereby resulting in vasoconstriction.[2,28] Polymorphonuclear leukocytes (PMNs) enter the wound area and act in the process of phagocytosis.[28] Fibroblasts are involved in the final stages of inflammation and early proliferation and play the most important role in the remodeling phase.[5–7] Fibroblasts are responsible for producing most of the ECM.[9,10] ECM secreted by fibroblasts can enhance tissue regeneration, including bone tissue.[4] Fibroblasts form granulation tissue to improve tissue integrity.[17] After wound closure, the activity level of fibroblasts decreases to produce wound tensile strength, so the size of the wound becomes smaller.[7]

Osteoblasts are crucial cells involved in the formation of new bone during both the proliferation and remodeling phases. Osteoblasts produce a bone matrix called osteoid.[5] Osteoblasts participate in the process of forming new bone by secreting organic components of the bone matrix such as type I collagen, osteocalcin, osteoid, and alkaline phosphatase.[29] In the process of hard tissue healing, the blood clot is replaced by granulation tissue or what is called soft callus (temporary callus); the soft callus will

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then be mineralized by chondrocytes and turn into hard callus (woven bone).[30] Subsequently, osteoblastic and osteoclastic activity remodels the woven bone, facilitating the development of mature lamellar bone.[29,30]

The wound begins to contract about seven days after its occurrence, when fibroblasts differentiate into myofibroblasts to produce smaller wounds, and generally, the wound heals completely and is closed by day 14. In this study, the Mobe leaf extract gel group had a smaller RSV value on days 3, 7, and 14 compared to the control group, so it can be assumed that the healing of wounds in the 3% Mobe leaf extract gel group was better than that of the Aloclair® gel group. According to the research conducted by Hanafiah et al.[19] 3% Mobe leaf extract gel has the best ability to accelerate wound healing both clinically and microscopically. This is influenced by the role of secondary metabolites from the Mobe leaf extract, which have anti-inflammatory, antibacterial effects and antioxidants, which can accelerate the wound healing process.[31]

The formation of fibroblasts was initiated on day 3 and peaked by day 7, followed by a decline in fibroblast numbers as osteoblasts took on the role of collagen production for the formation of the new alveolar bone.[8,32] In this study, the 3% Mobe leaf extract gel group exhibited the highest number of fibroblast cells on day 7 compared to the control group. However, by the 14th day, the 3% Mobe leaf extract gel group displayed the lowest number of fibroblast cells compared to the control group. It can be assumed that a decrease in fibroblasts on day 14 indicates good early formation of bone tissue, because good fibroblast proliferation can trigger effective new bone formation in the socket.[8,32]

Research conducted by Hakim et al.[33] revealed that the predominant secondary metabolites found in Mobe plants are flavonoids. Flavonoids are known for their anti-inflammatory properties, achieved through the inhibition of free radical activity and enhancement of epithelialization, which consequently accelerates wound healing by promoting increased fibroblast proliferation.[7] In addition, flavonoids play a role in increasing bone cell viability and bone density.[34,35] Flavonoids also play a role in the proliferation and tissue remodeling phase by increasing vascularization so that there is maximal supply of oxygen and nutrients to the injured cell tissue. Thus, there is an increase in collagen synthesis, thereby accelerating the wound healing process.[17,33,36]

Osteoblasts initiate formation on the 7th day following tooth extraction and continue to proliferate until the 14th day. From the 15th to the 28th day post extraction, osteoblasts undergo maturation and differentiate into osteocytes.[5] In this study, the group treated with 3% Mobe leaf extract gel exhibited the highest count of osteoblast cells on the 7th and 14th days compared to the control groups. Based on the research conducted by Hutabarat et al.,[37] saponins help wound healing by increasing the secretion of growth factors such as fibroblast growth factor (FGF), TGF-α, and vascular endothelial growth factor (VEGF). This is because saponins are able to stimulate monocyte proliferation so that the number of macrophages increases. These growth factors stimulate the migration, proliferation, and differentiation of osteoblasts so that new bone formation takes place more quickly.

Osteocytes are osteoblasts trapped in the bone matrix.[29] In this study, the group treated with 3% Mobe leaf extract gel displayed the highest count of osteocyte cells on the 28th day compared to the control groups. This result is probably due to the presence of secondary metabolites, such as Artocarpine, in Mobe leaf. Research by Yeh et al.,[18] showed that artocarpine can induce an early inflammatory phase by increasing migration of neutrophils and macrophages. It can also increase fibroblast and keratinocyte proliferation, accelerate epithelialization and collagen deposition, and increase myofibroblasts differentiation, which results in an increased wound contraction and increased TGF-β production. TGF-β can increase the migration and proliferation of osteoblast cells and facilitates maturation of osteoblasts into osteocytes, which further accelerates hard tissue healing.[29]

In this study, the positive control group utilized Aloclair® gel, which contains aloe vera. Research conducted by Sari et al.,[38] shows that aloe vera can help accelerate wound healing by reducing inflammation, stimulating collagen formation, fibroblast proliferation, stimulating the preparation of basic substances in the wound area, and re-epithelialization. However, Aloclair® gel also contains polyvinylpyrrolidone (PVP), which is known to cause allergic reactions in humans.[38] From this study, it can be concluded that 3% Mobe leaf extract gel has a better ability than Aloclair® gel in healing post-tooth extraction socket wounds in Wistar rats, due to a decrease in the clinical wound size of the extraction socket and an increase in the number of fibroblasts, osteoblasts, and osteocytes.

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