

**THE EFFECT OF ORAL RAMBUTAN HONEY ON ALKALINE PHOSPHATASE ACTIVITY IN DENTAL SOCKET WOUNDS HEALING PROCESS (IN VIVO)**  
*(EFEK MADU RAMBUTAN ORAL PADA AKTIVITAS ALKALI FOSFATASE PADA PROSES PENYEMBUHAN LUKA SOKET GIGI (IN VIVO))*

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**ABSTRACT**

Tooth extraction is a procedure that causes injury to the dental socket, requiring a proper healing process. Rambutan honey contains flavonoids and calcium, which have been reported to accelerate wound healing by increasing alkaline phosphatase (ALP) activity in blood serum. This study aimed to analyze the effect of oral rambutan honey on ALP activity during dental socket wound healing. This laboratory experimental study involved 20 rabbits that underwent lower right incisor extraction. The subjects were divided into five groups: negative control, positive control, and three treatment groups. The positive control group received 255 mg of calcium, while the treatment groups were administered rambutan honey at doses of 0.7 mL (treatment 1), 1.4 mL (treatment 2), and 2.1 mL (treatment 3). Observations were conducted on days 0, 7, 14, and 40 to assess ALP activity levels. Data analysis was performed using ANOVA followed by the Post Hoc Tukey test, while the Kruskal-Wallis test was followed by the Mann-Whitney test. The results showed that oral administration of rambutan honey

significantly increased ALP activity on days 7, 14, and 40 ( $p < 0.05$ ). Among the tested doses, 0.7 mL was the most effective, as it promoted a rise in ALP activity within normal physiological limits. Oral rambutan honey has a significant impact on enhancing ALP activity during dental socket wound healing, suggesting its potential as a natural therapeutic agent for post-extraction recovery.

**Keywords:** Alkaline Phosphatase (ALP), Rambutan Honey, Tooth Extraction, Wound Healing

### **ABSTRAK**

*Pencabutan gigi adalah prosedur yang menyebabkan cedera pada soket gigi, sehingga membutuhkan proses penyembuhan yang tepat. Madu rambutan mengandung flavonoid dan kalsium, yang dilaporkan dapat mempercepat penyembuhan luka dengan meningkatkan aktivitas alkali fosfatase (ALP) dalam serum darah. Penelitian ini bertujuan untuk menganalisis pengaruh madu rambutan oral terhadap aktivitas ALP selama penyembuhan luka soket gigi. Studi eksperimental laboratorium ini melibatkan 20 kelinci yang menjalani pencabutan gigi seri bawah kanan. Subjek dibagi menjadi lima kelompok: kontrol negatif, kontrol positif, dan tiga kelompok perlakuan. Kelompok kontrol positif menerima 255 mg kalsium, sedangkan kelompok perlakuan diberikan madu rambutan dengan dosis 0,7 mL (perlakuan 1), 1,4 mL (perlakuan 2), dan 2,1 mL (perlakuan 3). Observasi dilakukan pada hari ke-0, 7, 14, dan 40 untuk menilai tingkat aktivitas ALP. Analisis data dilakukan menggunakan ANOVA diikuti dengan uji Post Hoc Tukey, sedangkan uji Mann-Whitney diikuti dengan uji Kruskal-Wallis. Hasil penelitian menunjukkan bahwa pemberian madu rambutan secara oral secara signifikan meningkatkan aktivitas ALP pada hari ke-7, 14, dan 40 ( $p < 0,05$ ). Di antara dosis yang diuji, 0,7 mL adalah yang paling efektif, karena mendorong peningkatan aktivitas ALP dalam batas fisiologis normal. Madu rambutan oral memiliki dampak signifikan dalam meningkatkan aktivitas ALP selama penyembuhan luka soket gigi,*

*menunjukkan potensinya sebagai agen terapeutik alami untuk pemulihan pasca pencabutan gigi.*

***Kata kunci:*** Alkaline Fosfatase, Madu Rambutan, Pencabutan Gigi, Penyembuhan Luka

## INTRODUCTION

Tooth extraction is a traumatic dental procedure involving the removal of a tooth from its socket, affecting the gingiva, periodontal ligament, cementum, and alveolar bone.<sup>1,2</sup> Impaired wound healing is a recognized post-extraction complication. Physiologically, wound healing proceeds through overlapping phases of hemostasis, inflammation, proliferation, and remodeling, while post-extraction socket healing is characterized by blood clot formation, bone formation, and subsequent bone remodeling.<sup>3-5</sup>

Following extraction, vascular rupture in the periosteum induces bleeding on day 0. By day 7, fibrous tissue covers the socket surface, accompanied by osteoclast accumulation and initial osteoid formation. Reparative bone formation begins around day 14 and progresses through trabecular development and osteoid deposition along the alveolar bone, continuing until mature bone formation and remodeling are completed by approximately day 60.<sup>6,7</sup>

Bone remodeling is regulated by the coordinated activity of osteoblasts and

osteoclasts.<sup>8</sup> Active osteoblasts secrete osteoid and produce alkaline phosphatase (ALP), an enzyme essential for mineralization through the deposition of calcium and phosphate ions. ALP activity increases during osteoblast differentiation and decreases as mineralization progresses, and may also be influenced by physiological conditions and metal ions such as calcium, zinc, and magnesium.<sup>9,10</sup>

Calcium, a major inorganic component of bone, plays a critical role in inhibiting bone resorption and promoting bone formation.<sup>11,12</sup> ALP facilitates an alkaline environment within osteoid tissue, enabling calcium deposition and subsequent binding with phosphate to form hydroxyapatite crystals, which ultimately determine bone quality.<sup>13,14</sup>

In recent years, there has been growing interest in natural agents for wound healing due to their safety and cost-effectiveness. Rambutan honey, a monofloral honey, is known to accelerate wound healing owing to its high content of flavonoids (rutin group), vitamin C, and calcium, and its demonstrated antioxidant

activity *in vitro* and *in vivo*.<sup>15,16</sup> Oral honey consumption has been reported to support healing at doses equivalent to 20 mL per administration.<sup>17</sup> Topical rambutan honey (1 mL) has been reported to accelerate wound healing compared with 10% povidone-iodine, without significantly affecting ALP levels.<sup>18</sup> However, its effects on bone healing remain unclear. Therefore, this study investigated the effect of oral rambutan honey on alkaline phosphatase activity during post-extraction socket healing in rabbits.

## METHOD

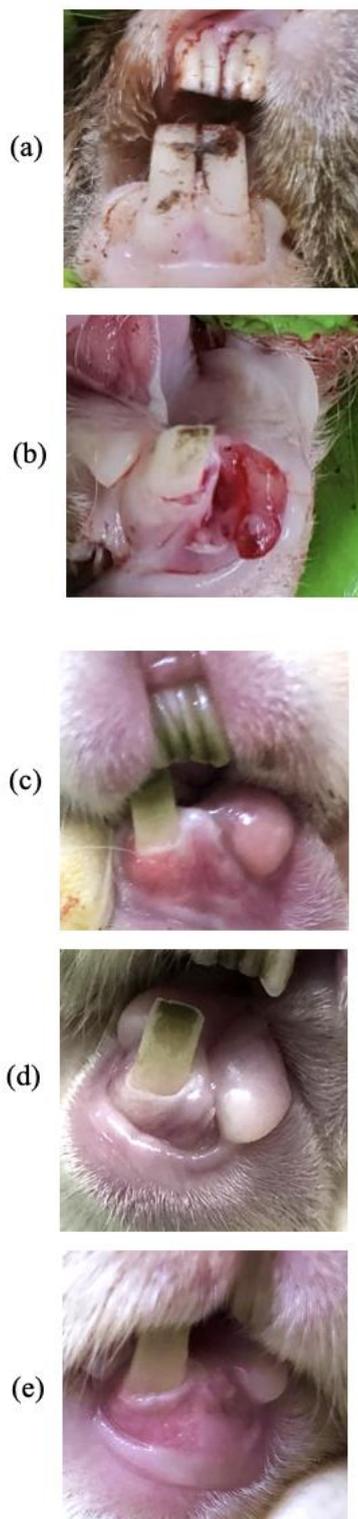
This analytical laboratory experimental study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran (No. 1227/UN6.KEP/EC/2018). The study evaluated the effect of oral rambutan honey on alkaline phosphatase (ALP) activity during tooth socket wound healing in rabbits. A minimum of 25 male rabbits was determined using the Federer formula and obtained from the Biofarma animal facility. Inclusion criteria were age 3–4 months, body weight 1000–1500 g, presence of the lower right incisor, and good general health. Rabbits with anatomical abnormalities, passive behavior, or  $\geq 20\%$  body-weight loss were excluded.<sup>18</sup>

Animals were randomly assigned into five groups: control (no treatment), calcium (255 mg twice daily), and three treatment groups receiving oral rambutan honey at doses of I: 0.7 mL, II: 1.4 mL, or III: 2.1 mL. All animals underwent the extraction of the lower right incisor. Blood samples (2.0–2.5 mL) were collected on days 0, 7, 14, and 40, centrifuged to obtain serum, and analyzed for ALP activity using reagents kit. Absorbance was measured spectrophotometrically. All experiments were performed in triplicate.<sup>15,16</sup>

Statistical analysis was performed using statistical software ( $p < 0.05$ ). Data normality was assessed by the Shapiro–Wilk test; normally distributed data were analyzed by one-way ANOVA with Tukey’s post hoc test, and non-parametric data by the Kruskal–Wallis test followed by Mann–Whitney analysis.

## RESULT

Twenty rabbits underwent extraction of the right mandibular incisor, and socket healing was evaluated clinically before extraction and on days 0, 7, 14, and 40 post-extraction (Figure 1).



**Figure 1.** (a) Condition of the rabbit's mucosa before the extraction of the lower right incisor; (b) Condition of the rabbit's tooth socket on day 0; (c) Condition of the rabbit's tooth socket on day 7; (d) Condition of the rabbit's tooth socket on

day 14; (e) Condition of the rabbit's tooth socket on day 40.

As shown in Figure 1, wound healing progressed progressively at each observation time point. The healing process of rabbit tooth socket wounds can be clinically observed from the wound diameter measured using calipers. Wound healing was assessed by measuring socket diameter using calipers, with mean values summarized in Table 1.

**Table 1.** Average diameter of rabbit tooth socket wounds on days 0, 7, 14, and 40

Group	Diameter of socket (mm)			
	Day-0	Day-7	Day-14	Day-40
Control	3.95	2.80	0.20	0
Calcium	3.83	2.73	0.08	0
I: 0.7 mL	3.90	2.50	0.03	0
II: 1.4 mL	3.83	2.58	0.05	0
III: 2.1 mL	3.78	2.45	0.05	0

A progressive reduction in socket diameter was observed in all groups over time. On day 14, the 0.7 mL rambutan honey group exhibited the smallest mean socket diameter, indicating faster wound closure compared with other treatments. By day 40, complete socket closure was observed in all groups. Alkaline phosphatase (ALP) activity measured on days 0, 7, 14, and 40 is presented in Table 2.

**Table 2.** Effect of rambutan honey on alkaline phosphatase activity on days 0, 7, 14, and 40

Alkaline Phosphatase	Statistical Test	N	p-value
Day-0	-	-	-
Day-7	One-way ANOVA	20	0,000*
Day-14	Kruskal-Wallis	20	0,021*
Day-40	One-way ANOVA	20	0,000*

\*p < 0.05 indicates a statistically significant difference.

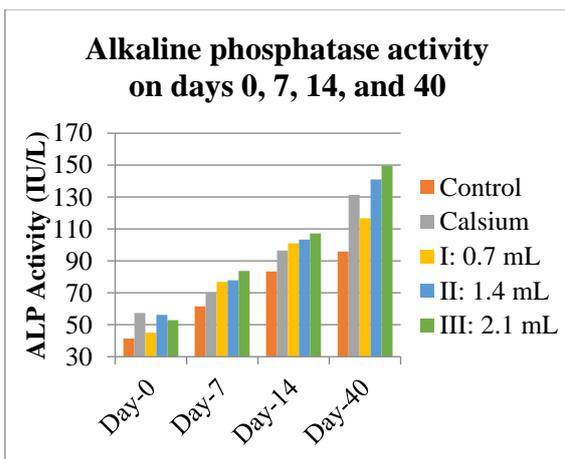
ALP activity on day 0 was not analyzed due to the absence of treatment exposure. Significant differences among groups were detected on day 7 (one-way ANOVA, p < 0.001), day 14 (Kruskal–Wallis, p = 0.021), and day 40 (one-way ANOVA, p < 0.001), indicating treatment-related modulation of ALP activity during healing. Dose-related effects of rambutan honey on ALP activity are detailed in Table 3.

**Table 3.** Differences in ALP activity on days 0, 7, 14, and 40

Group	Day-0	Day-7	Day-14	Day-40
	P-value	P-value	P-value	P-value
Control vs Calsium	0.021*	0.104	0.021*	0,000*
Control vs I: 0.7 mL	0.663	0.001*	0.021*	0.002*
Control vs II: 1.4 mL	0.020*	0.001*	0.021*	0.000*
Control vs III: 2.1 mL	0.021*	0.000*	0.021*	0.000*

Calsium vs I: 0.7 mL	0.043*	0.206	0.309	0.029*
Calsium vs II: 1.4 mL	0.237	0.127	0.248	0.229
Calsium vs III: 2.1 mL	0.043*	0.004*	0.248	0.006*
I: 0,7 mL vs II: 1,4 mL	0.042*	0.998	0.309	0.000*
I: 0,7 mL vs III: 2,1 mL	0.248	0.247	0.110	0.000*
II: 1,4 mL vs III: 2,1 mL	0.058	0.375	0.110	0.331

On day 7, Tukey’s post hoc analysis revealed significantly higher ALP activity in all rambutan honey groups compared with the control (p ≤ 0.001), and in the 2.1 mL honey group compared with the calcium group (p = 0.004). On day 14, Mann–Whitney analysis showed significant differences between the control and all honey-treated groups (p = 0.021). By day 40, most group comparisons remained significant, although no differences were observed between the calcium and 1.4 mL honey groups (p = 0.229) or between the 1.4 mL and 2.1 mL honey groups (p = 0.331). The difference in ALP absorbance values at each time point can be seen in Figure 2.



**Figure 2.** Differences in the average absorbance values of alkaline phosphatase activity on days 0, 7, 14, and 40.

Figure 2 shows the increase in ALP activity absorbance values from day 0 to day 40 in each group. Day 40 showed that the calcium group, the 1.4 mL rambutan honey group, and the 2.1 mL rambutan honey group had ALP values above the normal limit of 35–123 IU/L.

## DISCUSSION

Post-extraction socket healing begins with hemostasis and early inflammation, typically lasting 3–5 days, during which clot formation and inflammatory cell recruitment establish the foundation for subsequent bone repair.<sup>1-3</sup> Alkaline phosphatase (ALP) is a recognized marker of osteoblast activity and early bone formation; moderate elevations in ALP within physiological ranges reflect controlled osteogenic processes, whereas

excessive increases may indicate pathological conditions.<sup>19,20</sup>

In this study, oral administration of 0.7 mL rambutan honey was associated with significant increases in serum ALP activity within the normal reference range during key healing intervals. These findings suggest that this dose may support osteogenic activity during the proliferative and reparative phases without inducing excessive enzymatic activity. Observed ALP trajectories align with previous reports linking moderate ALP elevations to active bone formation and early mineralization.<sup>21,22</sup>

Rambutan honey contains flavonoids, vitamin C, calcium, and magnesium, compounds with documented anti-inflammatory, antioxidant, and bone-modulating effects.<sup>15,16,18</sup> Calcium contributes to hydroxyapatite crystallization, and magnesium enhances osteoblast proliferation and differentiation, which may underlie the observed ALP modulation and accelerated wound closure.<sup>23-25</sup> This integrated bioactivity likely facilitates a more favorable healing environment compared with untreated controls.

While higher doses of rambutan honey also increased ALP activity, the 0.7 mL dose achieved the most consistent increase within physiological limits,

supporting its potential as an adjunct in post-extraction bone healing. This finding is consistent with studies demonstrating dose-dependent effects of natural bioactive compounds on bone remodeling markers.<sup>25,26</sup>

This study relied on serum ALP as a surrogate marker of bone activity without histological or molecular validation at the extraction site. The sample size, while statistically calculated, was limited, and additional bone markers (e.g., osteocalcin, RUNX2) were not assessed. Moreover, species differences in healing biology warrant caution when extrapolating these results to human clinical practice. Future research should incorporate site-specific histomorphometry and expanded molecular profiling to validate and extend these findings.

## CONCLUSION

Oral administration of rambutan honey was associated with significant changes in alkaline phosphatase (ALP) activity during post-extraction socket healing on days 7, 14, and 40. Among the tested doses, 0.7 mL administered twice daily showed the most favorable profile, characterized by a reduction in socket wound area and an increase in ALP activity that remained within physiological limits,

suggesting a potential supportive role in the post-extraction healing process.

## CONFLICT OF INTEREST

We declare that there is no conflict of interest in the scientific articles.

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