

Effect of Rambutan Honey Administration on Neovascularization and Fibroblast Proliferation in Colonic Anastomosis: An Experimental Study in New Zealand White Rabbits.

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ABSTRACT

Background: Anastomotic leakage remains a major complication after colonic surgery, contributing to morbidity, mortality, and substantial healthcare costs. Honey has demonstrated antimicrobial, anti-inflammatory, and pro-healing properties, but evidence regarding Indonesian local honey in internal intestinal anastomosis remains limited.

Objective: This study evaluated the effect of Indonesian rambutan honey (madu Rambutan) on fibroblast proliferation and neovascularization in colonic anastomosis tissue using a New Zealand White rabbit model.

Methods: A true experimental post-test-only control group design was conducted using 38 adult male New Zealand White rabbits (n=19/group). All animals underwent standardized colonic transection and end-to-end anastomosis using a single-layer interrupted technique. The treatment group received oral rambutan honey 2 g/kg/day for seven days, while controls received standard feed and water only. On postoperative day 7, anastomotic tissue was harvested and evaluated histologically using hematoxylin and eosin staining. Fibroblast quantity and neovascularization were assessed in five high-power fields and graded semi-quantitatively. Group comparisons were analyzed using the Mann-Whitney test.

Results: Baseline body weight was comparable between groups (p=1.00). The treatment group demonstrated significantly higher fibroblast scores (median 3 [IQR 2-3] vs. 2 [IQR 2-3], p=0.010) and neovascularization scores (median 2 [IQR 1-3] vs. 1 [IQR 1-2], p=0.004) compared with controls.

Conclusion: Indonesian rambutan honey significantly enhanced fibroblast proliferation and neovascularization in colonic anastomosis tissue on postoperative day 7, suggesting improved proliferative-phase healing...

Keywords: colonic anastomosis; anastomotic healing; rambutan honey; fibroblast; neovascularization; rabbit model

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INTRODUCTION

Colonic anastomosis is a fundamental surgical procedure that reconnects two bowel segments following resection or transection.¹ Despite advances in colorectal surgery, anastomotic leakage remains a major postoperative complication and continues to contribute substantially to morbidity and mortality. In Indonesia, reported leakage rates and associated mortality after colonic anastomosis remain considerable, ranging from 6% to 22% of cases. A 2024 study from Dr. Soetomo General Hospital, Surabaya, reported an anastomotic leak in 36.5% of colon cancer patients undergoing hemicolectomy.² Clinically, leakage can precipitate life-threatening sequelae, including peritonitis, intra-abdominal

abscess, and sepsis.^{3,4} Beyond its clinical impact, anastomotic leakage imposes a marked economic burden; the total cost including hospitalization has been estimated at USD 28.6 million per 1,000 patients.⁵

Multiple strategies have been explored to reduce leak incidence and to accelerate anastomotic healing, spanning perioperative optimization, postoperative care, and the use of healing agents such as honey, Aloe vera, and *Channa striata* (Haruan).⁶ Among these approaches, honey has a long-standing role in wound management and is increasingly supported by mechanistic and experimental evidence. Honey exerts antimicrobial effects through components such as hydrogen peroxide (H₂O₂) and phenolic compounds,

while its anti-inflammatory properties can facilitate progression from the inflammatory to the proliferative phase by modulating inflammatory mediators. In addition, honey may promote neovascularization by enhancing the expression of vascular endothelial growth factor (VEGF) and other growth factors implicated in angiogenesis, alongside improving nitric oxide (NO) bioavailability via bioactive compounds including flavonoids and polyphenols.⁷ At the cellular level, honey has been associated with regulation of immune cell activity and inflammatory signaling, including pathways involving TNF- α and interleukin- β , and with anti-inflammatory actions mediated in part by NO.⁸ Honey has also been reported to increase the expression of transforming growth factor beta (TGF- β) isoforms that are central to collagen synthesis and extracellular matrix deposition, while supporting fibroblast proliferation, migration, and differentiation through signaling pathways such as PI3K/Akt and MAPK, and via matrix metalloproteinase activity relevant to tissue remodeling.^{9,10}

The biological rationale for honey in anastomotic healing is aligned with the known phases of intestinal wound repair, which include inflammation, proliferation, and remodeling, with fibroblasts and angiogenesis playing pivotal roles during the proliferative phase. Adequate neovascularization is essential to ensure oxygen and nutrient delivery, support collagen synthesis by fibroblasts, and reduce the risk of dehiscence and leakage, particularly in settings of compromised perfusion.¹¹ Experimental data have suggested that honey can improve anastomotic outcomes: in rodents, honey accelerated anastomotic wound healing and in a Wistar rat model, Tualang honey significantly improved colonic anastomotic tensile strength and histopathological parameters, including fibroblast counts and inflammatory cell.^{12,13} Additional evidence indicates that certain honeys can stimulate fibroblast proliferation, potentially linked to hydrogen peroxide content.¹⁴

However, while honey has been widely investigated, studies specifically addressing Indonesian local honey remain limited. "Madu Rambutan" refers broadly to honey produced in Indonesia by local or locally foraging bees, and its characteristics may vary with floral source and bee species, influencing physicochemical properties and bioactivity.¹⁵ Rambutan honey is a prominent monofloral Indonesian honey produced by *Apis mellifera*.¹⁶ Its relatively high phenolic and flavonoid content is reported to contribute to antioxidant and anti-inflammatory effects, with candidate bioactive constituents including pinocembrin and pinobanksin,

which have been linked to redox regulation and fibroblast activity during wound repair.¹⁶ Experimental work has suggested that rambutan honey may reduce oxidative stress markers and induce TGF- β 1, supporting tissue repair processes.¹⁷ In addition, clinical and case-based reports on Indonesian honey have described enhanced granulation and epithelialization in chronic wounds without notable allergic reactions or secondary bacterial infection, alongside potential cost efficiency.^{15,18} Although these findings support a potential role for Indonesian honey in wound healing, direct evidence in internal intestinal anastomosis—particularly regarding neovascularization and fibroblast responses—remains scarce.

Therefore, this study aims to evaluate the effect of Indonesian rambutan honey (madu Rambutan) on colonic anastomotic healing by assessing neovascularization and fibroblast growth in a New Zealand rabbit model.

METHOD

This study used a true experimental *in vivo* post-test-only control group design to evaluate the effect of Indonesian local honey (madu Rambutan) on neovascularization and fibroblast quantity in colonic anastomosis. A total of 38 adult male New Zealand rabbits (1.5–2.0 kg) from a single species were obtained from a rabbit farm in Batu, East Java, and acclimatized for seven days under controlled housing conditions (sterile cages, 20–24°C, 40–70% humidity, 12-hour light/dark cycle). Rabbits were randomly allocated into two groups (n=19 each): a control group receiving standard feed and water only, and a treatment group receiving standard feed and water plus madu Rambutan. Sample size was determined using Federer's replication formula, resulting in a minimum of 16 rabbits per group, with an additional 20% added to anticipate losses.

All animals underwent standardized colonic transection and end-to-end anastomosis under strict aseptic technique at the Veterinary Medicine Faculty Laboratory, Universitas Airlangga (November 2025–January 2026). General anesthesia was induced with intramuscular ketamine 25 mg/kg, with premedication using sulfas atropine 0.2 mg/kg and diazepam 1 mg/kg. A 5 cm midline laparotomy was performed, the cecum was identified, and the colon was transected 5 cm distal to the cecum. Anastomosis was completed using a single-layer interrupted technique with 4-0 Vicryl, followed by abdominal closure with 4-0 Vicryl and postoperative abdominal

bandaging. Postoperatively, the treatment group received oral madu Rambutan 2 g/kg once daily via feeding tube each morning until postoperative day 7, while the control group received no honey.

On postoperative day 7, all rabbits were euthanized using a humane method approved by the ethics committee, and the abdomen was reopened to harvest a colonic segment containing the anastomosis (2.5 cm proximal and 2.5 cm distal). Specimens were fixed in 10% formalin and processed for histopathology. Slides were stained with hematoxylin and eosin (H&E) and evaluated under a light microscope (Olympus CX 23) at 400× magnification by a pathologist. Neovascularization and fibroblast counts were assessed in five randomly selected high-power fields per specimen and recorded as mean values. Neovascularization was graded as low (0-5 capillaries/field), moderate (6-10/field), or high

(>10/field). Fibroblast quantity was graded as low (0-10 cells/field), moderate (11-20/field), or high (>20/field).

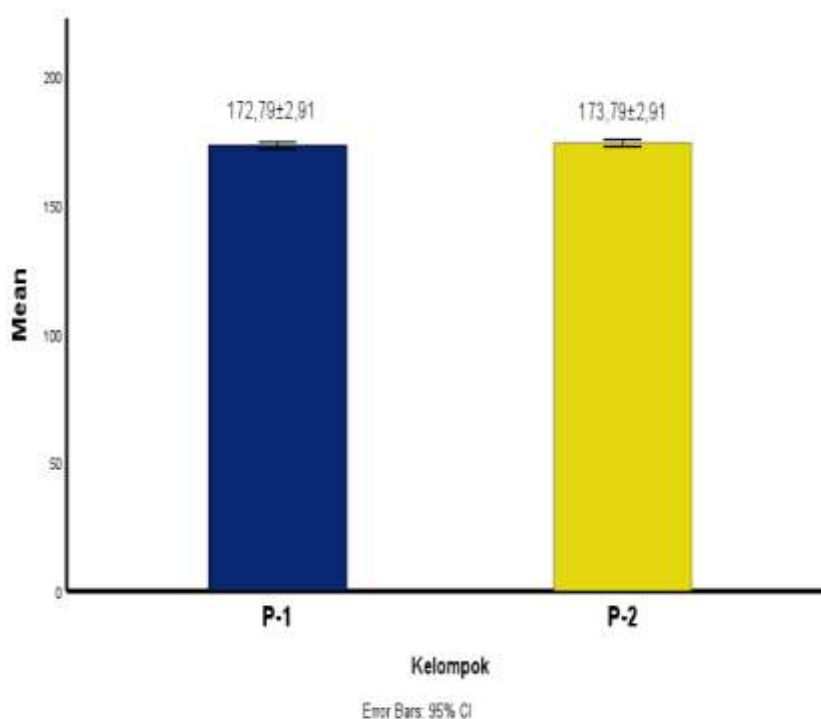
RESULTS

Baseline characteristics

A total of 38 adult male New Zealand White rabbits were included and equally allocated into the control group (P-1, n=19) and the treatment group (P-2, n=19). All animals remained in good general condition with normal behavior and activity during the observation period. The mean baseline body weight was comparable between groups (P-1: 172.79 ± 2.91 g; P-2: 173.79 ± 2.91 g), and the homogeneity test confirmed no significant difference (p=1.00), indicating that baseline body weight distribution was similar between groups (Table 1, Figure 1).

Characteristic	P-1 (n=19)	P-2 (n=19)	p-value
Rabbit strain	New Zealand White	New Zealand White	—
Sex	Male	Male	—
General condition	Good, normal behavior and activity	Good, normal behavior and activity	—
Baseline body weight (g), mean ± SD	172.79 ± 2.91	173.79 ± 2.91	1.00

Table 1. Baseline characteristics of experimental animals
Figure 1. Mean baseline body weight of rabbits by group



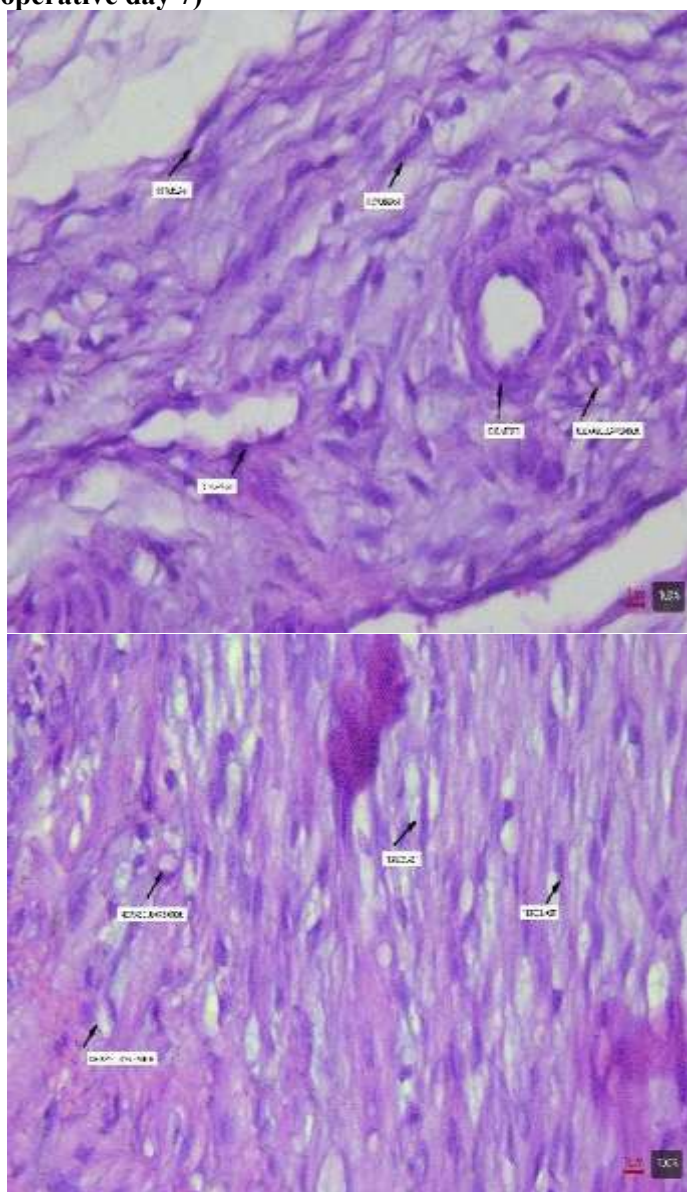
Mean baseline body weight was comparable between the control group (P-1) and the treatment group (P-2). Error bars represent 95% confidence intervals.

Histopathological findings

On postoperative day 7, hematoxylin and eosin (H&E) staining of colonic anastomosis tissue showed fibroblast proliferation and neovascular formation in both groups. Qualitatively, the control group (P-1) demonstrated fewer fibroblasts with less uniform distribution, accompanied by a looser stromal

structure and less organized collagen fibers. In contrast, the treatment group (P-2) showed denser and more evenly distributed fibroblasts around the anastomotic line, with a more compact stroma and collagen fibers beginning to align more regularly. Regarding vascular changes, P-1 was characterized by minimal neovascularization with predominance of mature vessels, whereas P-2 demonstrated a greater number of thin-walled newly formed capillaries distributed more widely in the stromal tissue (Figure 2).

Figure 2. Representative histopathological micrographs of fibroblasts and neovascularization in colonic anastomosis tissue (postoperative day 7)



(A) (B)
(A) Control group (P-1). (B) Treatment group (P-2). Hematoxylin and eosin (H&E) staining, 400× magnification.

Effect of Indonesian honey on fibroblast and neovascularization scores

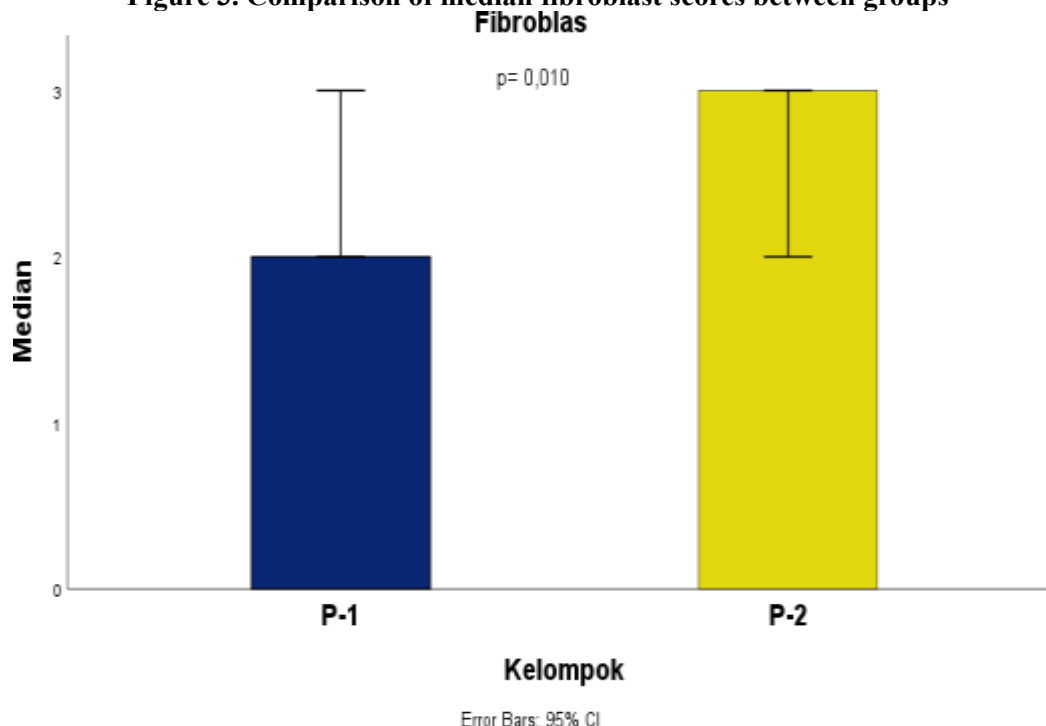
Semi-quantitative scoring showed significantly higher fibroblast and neovascularization scores in the treatment group. The median fibroblast score in P-1 was 2 (IQR 2-3), while in P-2 it increased to 3 (IQR 2-3), with a statistically significant difference (Mann-Whitney test, $p=0.010$). Similarly, the median neovascularization score was 1 (IQR 1-2) in P-1 and 2 (IQR 1-3) in P-2, also showing a significant difference ($p=0.004$). These findings indicate that administration of Indonesian rambutan honey significantly enhanced fibroblast proliferation and neovascularization at the anastomotic site on day 7 postoperatively (Table 2, Figures 3-4).

Table 2. Comparison of fibroblast and neovascularization scores in colonic anastomosis tissue (postoperative day 7)

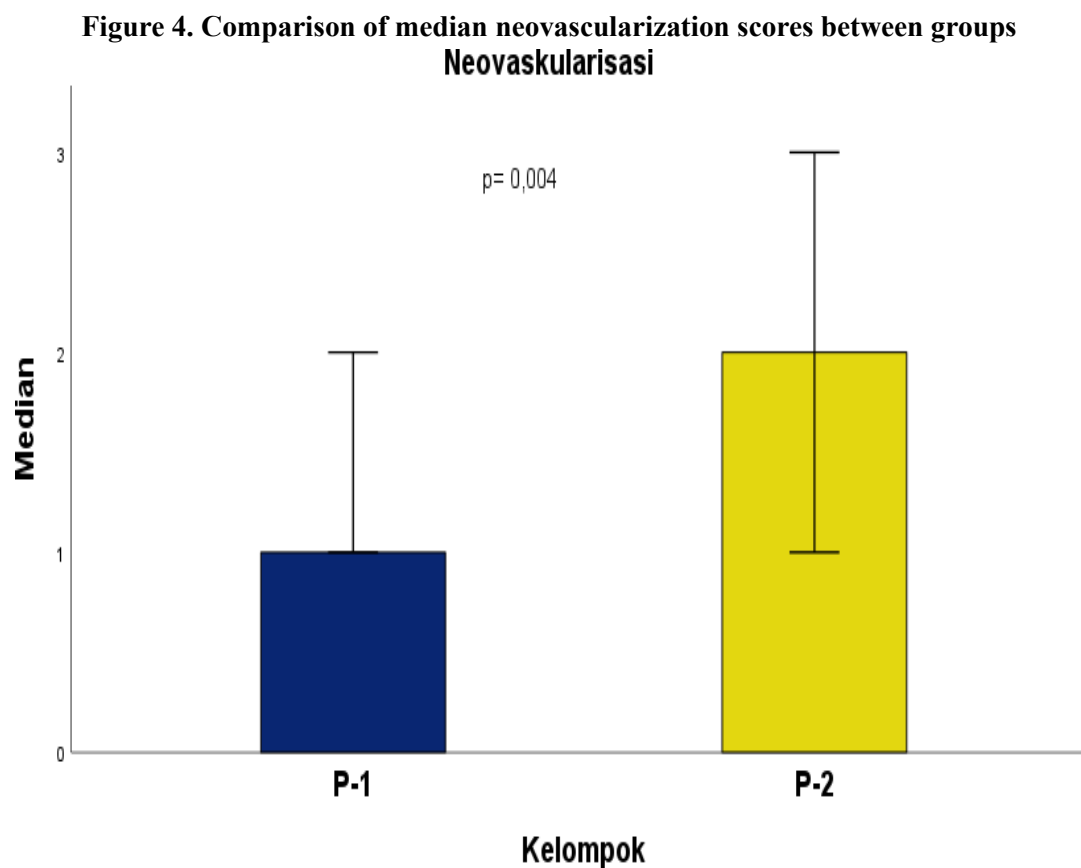
Variable	P-1 (Control)	P-2 (Honey)	p-value
Fibroblast score, median (IQR)	2 (2-3)	3 (2-3)	0.010*
Neovascularization score, median (IQR)	1 (1-2)	2 (1-3)	0.004*

*Statistically significant at $p<0.05$. Data are presented as median (IQR). Mann-Whitney test.

Figure 3. Comparison of median fibroblast scores between groups



Median fibroblast score was significantly higher in the treatment group (P-2) compared with the control group (P-1) ($p=0.010$). Error bars represent 95% confidence intervals.



Median neovascularization score was significantly higher in the treatment group (P-2) compared with the control group (P-1) ($p=0.004$). Error bars represent 95% confidence intervals.

DISCUSSION

Appropriate selection of an animal model is essential for strengthening internal validity and supporting generalizability in experimental research.¹⁹ Rabbits are commonly used in biomedical studies because of their short lifespan, rapid reproductive rate, and adaptability to environmental change. They are also less susceptible to relocation-related behavioral or genetic alterations than species requiring strict habitat conditions. Rabbits aged 4–7 months are considered suitable for experimental surgery because organs are fully developed, immune responses are relatively stable, and perioperative mortality is lower than in very young or aged animals.²⁰ New Zealand White rabbits are frequently used in gastrointestinal and wound-

healing models due to practical and biological advantages relevant to intestinal anastomosis research.²¹ Their body size facilitates consistent anastomotic construction and reproducible surgical manipulation. Although rabbit gastrointestinal anatomy differs from humans, functional similarity remains sufficient to investigate core mechanisms of anastomotic repair.¹¹ In the present study, baseline body weights were comparable between groups, supporting group homogeneity and reducing the likelihood of confounding from pre-intervention differences.

Fibroblasts are central to the proliferative phase of wound healing, migrating after inflammation and serving as the primary source of extracellular matrix (ECM) components required for granulation tissue formation.²² Collagen deposition is a key determinant of early anastomotic strength, with type III collagen predominating in early repair and subsequent remodeling toward type I collagen supporting long-term mechanical integrity.¹¹ In this study, histopathological evaluation on postoperative day 7 demonstrated increased fibroblast density and a

more compact stromal appearance in honey-treated rabbits compared with controls, supported by semi-quantitative scoring. This suggests a more advanced proliferative-phase response at the anastomotic site. These findings are consistent with wound-healing literature indicating that honey accelerates granulation tissue development, often reflected by increased fibroblast accumulation and earlier ECM formation.²³ Similar observations have been reported in intestinal anastomosis models; Aznan et al. showed improved tensile strength with significantly higher fibroblast counts in honey-treated animals.¹³ Supporting mechanistic evidence also indicates that Indonesian honey enhances fibroblast viability and migration *in vitro*.²⁴

Several mechanisms may explain the increased fibroblast response. Honey provides metabolic substrates (glucose and fructose) that may support proliferating reparative cells. Its antioxidant activity, largely derived from phenolic compounds and flavonoids, may reduce excessive oxidative stress and create a microenvironment favorable for fibroblast function and balanced ECM deposition. Honey's acidic pH and antimicrobial properties may further reduce bacterial burden, suppress protease activity, and preserve growth factors and ECM components. Honey has also been reported to modulate inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, which may indirectly support epithelial recovery and downstream collagen synthesis.²⁵

Angiogenesis is another critical determinant of colonic anastomotic healing because newly formed vessels restore perfusion and deliver oxygen and nutrients necessary for granulation tissue formation and tissue remodeling. Key mediators such as VEGF and FGF promote endothelial proliferation and migration and support restoration of submucosal vascularization, which is essential for anastomotic viability.¹¹ Postoperative hypoxia can activate HIF-1 α , increasing VEGF expression and driving neovascular development.²⁶⁻²⁸ In this study, honey-treated rabbits demonstrated significantly higher neovascularization scores on postoperative day 7 compared with controls, indicating more active angiogenesis during the

proliferative phase. This finding is consistent with evidence that honey can increase VEGF expression and enhance angiogenic responses. However, Aznan et al. reported improved fibroblast parameters without a significant neovascularization difference, which may relate to dosing differences.¹³

Mechanistically, honey-derived antioxidants, particularly flavonoids, may support angiogenesis through endothelial signaling pathways including MAPK and PI3K/Akt, potentially enhancing VEGF-related activity.²⁹ Reduction of oxidative stress may further improve endothelial responsiveness, and low concentrations of hydrogen peroxide naturally generated in honey may stimulate angiogenesis without cytotoxicity.³⁰

This study has limitations. Fibroblast proliferation and neovascularization were evaluated using semi-quantitative histopathological scoring, which is widely applied but inherently subjective and may reduce sensitivity for subtle differences. In addition, H&E staining provides structural assessment but does not characterize fibroblast phenotype or molecular activity. The study also did not differentiate collagen type I and III deposition or assess mechanistic markers such as α -SMA or TGF- β , limiting interpretation of ECM remodeling and fibroblast activation. Despite these limitations, the study provides histopathological evidence of improved proliferative-phase healing in honey-treated anastomoses, reflected by significantly higher fibroblast and neovascularization scores. These findings support a potential beneficial effect of Indonesian rambutan honey and justify future studies incorporating immunohistochemistry, gene expression profiling, and quantitative collagen analysis to better define underlying mechanisms and link histological outcomes with mechanical strength

CONCLUSION

Administration of Indonesian local honey (madu Rambutan) significantly increased fibroblast proliferation and neovascularization in colonic anastomosis tissue of New Zealand White rabbits on postoperative day 7, as reflected by higher

histopathological scores compared with the control group. Overall, these findings indicate that madu Rambutan supports colonic anastomotic healing by enhancing key components of the proliferative phase, particularly fibroblast activity and new blood vessel formation at the anastomotic site.

Future studies are recommended to incorporate immunohistochemistry and molecular approaches (e.g., α -SMA, VEGF, TGF- β , and collagen type I/III) to more specifically characterize fibroblast activation, angiogenic signaling, and extracellular matrix remodeling. Further investigation using different honey doses and longer observation periods is also needed to determine the optimal dosage and to better describe the healing dynamics of colonic anastomosis across multiple wound-healing phases.

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