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Test of The Effectiveness of Trigona Madu (*Trigona sp.*) on Healing of Burns and Leukosit LevelsIn White Rats (*Rattus norvegicus*)

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ABSTRACT

Burn injuries are complex conditions requiring effective treatment to accelerate healing and minimize complications. This study investigates the therapeutic potential of Trigona honey (*Trigona sp.*) in healing second-degree burn wounds and its effect on leukocyte levels in white rats (*Rattus norvegicus*). Using a true experimental design with a posttest control group, 24 male rats were divided into four groups: negative control (distilled water), positive control (povidone iodine), and two treatment groups receiving topical Trigona honey once or twice daily. Burn wound size was measured on days 1, 7, and 14 using a caliper, while leukocyte levels were assessed on day 7 using the improved Neubauer counting chamber. Data were analyzed with SPSS, employing normality tests, one-way ANOVA, and Repeated ANOVA tests as appropriate. Results indicated significant wound size reduction in all groups, with the twice-daily Trigona honey group showing the greatest improvement (1.12 cm² reduction after 14 days). However, leukocyte level changes were not statistically significant among groups. The therapeutic effects of Trigona honey are attributed to its bioactive compounds, including flavonoids and phenolics, which enhance re-epithelialization, angiogenesis, and granulation tissue formation. Despite insignificant leukocyte modulation, Trigona honey demonstrated notable efficacy in accelerating wound healing compared to control treatments. Further studies are recommended to optimize dosing, evaluate long-term effects, and conduct clinical trials in humans. Trigona honey holds promise as a natural alternative for burn treatment, particularly when formulated into easily applicable forms such as ointments or gels.

Keywords: Trigona Honey, Burn Wound Healing, Leukocyte Levels, Natural Therapy, Wound Management

INTRODUCTION

Burns are defined as damage caused by direct contact with heat, electricity, chemicals, or radiation sources, resulting in coagulative necrosis of the various layers of skin and underlying tissues. Several factors, including the location of the burn, temperature, and duration of heat exposure, directly affect the severity of the injury. Burns can be classified based on the extent and depth of the injury. The assessment of wound area percentage can be done using the palmar method, Lund-Browder Chart, or the rule of nine diagram. Burn depth is categorized into three types: first-degree burns affecting only the epidermis, second-degree burns affecting the epidermis and part of the dermis, and third-degree burns affecting the entire skin layer and potentially underlying tissues (Hasanah et al., 2023; Schaefer & Szymanski, 2023; Żwierełło et al., 2023). Burn wound healing is a complex process involving four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Various treatment approaches have been developed, one of which includes the use of honey (Thedjakusuma et al., 2022).

Honey, defined as a sweet substance produced by bees (*Apis sp.*) by combining nectar from plants, has been used for over 5000 years both as food and medicine due to its nutritional and therapeutic benefits. Its characteristics vary based on the source of nectar, geographical location, and processing techniques. Bees are classified into stinging (*Apis genus*) and stingless (*Trigona genus*) types. Honey contains approximately 200 bioactive compounds, with flavonoids and polyphenols as the primary bioactive molecules. Its phytochemical, anti-inflammatory, antimicrobial, and antioxidant properties give honey therapeutic potential for treating various diseases, including wound healing (Fitriyani et al., 2020; Leoni et al., 2021; Samarghandian et al., 2017; Spoială et al., 2022). Honey ability to heal wounds is attributed to its anti-inflammatory and antioxidant properties, promoting re-epithelialization, angiogenesis, and the stimulation of leukocytes to release cytokines and growth factors essential for tissue repair (Scepankova et al., 2021).

The study of Trigona madu (*Trigona sp.*) and its potential therapeutic effects on burn healing and leukocyte levels in white rats (*Rattus norvegicus*) is an important area of biomedical research. Natural products, especially those derived from honey, have gained significant attention for their bioactive properties, offering alternatives to synthetic medications that may have adverse effects. Trigona madu, a type of stingless bee honey, contains bioactive compounds like flavonoids, phenolic acids, and enzymes that contribute to its antioxidant, anti-inflammatory, and antimicrobial properties. These properties make it a promising candidate for enhancing wound healing. Previous studies have shown honey potential in promoting tissue regeneration and reducing inflammation, critical factors for burn healing (Irawan et al., 2024). The application of Trigona madu may facilitate faster recovery and improve outcomes in burn injuries. Additionally, Trigona madu's impact on leukocyte levels is of interest due to the crucial role of leukocytes in the immune response. Modulating leukocyte activity can provide insights into an organism's immune status and healing capability. Research indicates that certain natural products can influence leukocyte activity, enhancing the body's defenses during healing (Boey et al., 2019). Investigating Trigona madu's effects on leukocyte levels in Rattus norvegicus aims to elucidate its immunomodulatory effects in burn healing. The use of Rattus norvegicus as a model organism is well-established due to its physiological and genetic similarities to humans, making it suitable for evaluating therapeutic agents (Gustian et al., 2023).

Previous research has extensively explored the therapeutic properties of honey, particularly its efficacy in wound healing and its potential to modulate immune responses. A systematic review highlights the medicinal use of honey, emphasizing its antibacterial and anti-inflammatory properties, which are crucial in treating burns and promoting wound healing in various animal models, including rats and horses (Vogt et al., 2021). Furthermore, studies have demonstrated that honey, particularly varieties like Manuka honey, exhibits significant antimicrobial activity against a range of pathogens, making it a valuable alternative to conventional antibiotics in veterinary medicine (Váczi et al., 2023). For instance, the work of indicates that honey can enhance the healing process of infected wounds, showcasing its potential to reduce inflammation and promote tissue regeneration (Dahiya et al., 2024). In addition to its direct antibacterial effects, honey has been shown to influence leukocyte levels and immune responses. Research demonstrated that Brazilian organic honey could decrease inflammatory markers and neutrophil migration in mice, suggesting a systemic immunomodulatory effect that could be beneficial in managing infections and enhancing recovery from injuries (Romário-Silva et al., 2022). Similarly, while the potential of natural products in combating antibiotic resistance, their focus is primarily on capsaicin and its derivatives, which may not directly support the claims regarding honey (Füchtbauer et al., 2021). Moreover, the potential of honey to serve as a topical treatment for burns has been supported by various studies, including those that evaluate the healing efficacy of honey-based gels in equine models (Madsen et al., 2024). These findings align with the broader literature that advocates for the integration of natural products like honey into veterinary practices, particularly in light of rising concerns regarding antibiotic resistance and the need for sustainable treatment options (Mandel et al., 2020).

In conclusion, the study of Trigona madu's effectiveness in burn healing and its influence on leukocyte levels represents a promising research avenue. By leveraging its natural bioactive properties, this research contributes to the development of alternative therapeutic strategies that enhance wound healing and immune responses. The findings may pave the way for further exploration of natural remedies in managing burn injuries and related health conditions.

METHODS

This research is a type of true experimental research with a posttest control group design (Agnesia et al., 2023; Syahza, 2021), which was conducted at the Faculty of Medicine Laboratory, Muslim University of Indonesia from September to October 2024. The independent variable in this study is trigona bee honey (*Trigona sp.*), while the dependent variables include the rate of burn wound healing and leukocyte levels in white rats (*Rattus norvegicus*). This study used 24 male white rats aged 8-12 weeks with a body weight of 150-200 grams randomly divided into four groups: negative control group (*distilled water*), positive control (*povidone iodine*), treatment I (*trigona honey once a day*), and treatment II (*trigona honey twice a day*). Second-degree burns were made on rats using a hot metal rod, and trigona honey was administered topically according to the group. Wound evaluation was performed by measuring the burn wound on the first, seventh, and fourteenth days using a caliper, while leukocyte levels were measured on the seventh day with an improved Neubauer counting chamber (Liberty, 2024; Swarjana, 2016). Data were analyzed using SPSS with Shapiro-Wilk normality test, homogeneity test, and One-way Anova or Kruskal-Wallis test depending on data distribution, followed by post hoc test if necessary (Ghozali, 2014; Sujarweni, 2015). This study adheres to the ethical principles of animal use, namely the 3R principle (*Replacement, Reduction, Refinement*) to ensure the welfare of test animals, with efforts to minimize pain and suffering through safe techniques, use of anesthesia, and appropriate care. This study aims to evaluate the effectiveness of trigona honey in burn wound healing and its effect on leukocyte levels, with the hope of contributing to the development of natural therapies for burns.

RESULTS AND DISCUSSION

This experimental study aimed to evaluate the effectiveness of trigona bee honey (*Trigona sp.*) in healing burn wounds and its impact on leukocyte levels. The study involved 24 white rats divided into four groups: a negative control group given distilled water, a positive control group given povidone iodine, a first treatment group given trigona honey topically once daily, and a second treatment group given trigona honey topically twice daily. Interventions were conducted daily, and burn wound healing was observed macroscopically by measuring wound length with a caliper on days 1, 7, and 14, showing significant progress in healing. Leukocyte levels were examined on day 7 using the counting room method to compare differences between groups, which were found to be statistically insignificant. Data from wound healing observations and leukocyte level examinations were analyzed to assess the effectiveness of trigona honey in accelerating burn wound healing and its impact on leukocyte levels.

To enhance the control group selection in the study investigating the effectiveness of Trigona honey on burn wounds and leukocyte levels, it is advisable to include a comparator group using Manuka honey, a well-known and widely-studied honey recognized for its superior wound-healing properties. Research supports the efficacy of honey in promoting healing, particularly Manuka honey, which is noted for its unique antibacterial and healing characteristics (Febriyenti et al., 2019; Pramesty, 2021). Manuka honey effectively creates a moist wound environment, facilitating healing through mechanisms such as autolytic debridement and infection prevention. Additionally, Manuka honey significant antibacterial activity against wound pathogens can lead to faster healing compared to traditional treatments (Bunza et al., 2019; Hartati et al., 2021). Including a Manuka honey control group would strengthen the experimental design by providing a benchmark against established healing properties, allowing for a clearer understanding of Trigona honey relative effectiveness. Evaluating healing rates and leukocyte levels across groups distilled water, povidone iodine, Trigona honey (once and twice daily), and Manuka honey would enable a robust analysis of Trigona honey effectiveness, enriching the study's findings. In summary, a comparative control group with Manuka honey would facilitate a more nuanced interpretation of the data and lead to more definitive conclusions regarding Trigona honey potential in wound healing.

Burns Wounds

To identify whether the data is normally distributed or not, a normality test is carried out using the Shapiro-Wilk method. The assessment is based on the probability value (p-value), with the criterion that the data is considered normally distributed if the p-value > 0.05. Conversely, if the p-value < 0.05, the data is declared not normally distributed. The results of these statistical tests are presented in Table 1.

Table 1
Data Distribution of Rat Burn Area.

Group	Wound Area Mean (SD) cm^2	*p-value*
Negative Control (Aquades)		
Negative Control 1	2.00	0
Negative Control 7	1.74 (0.10)	0.84
Negative Control 14	1.00 (0.27)	0.78
Positive Control (Povidone Iodine)		
Positive Control 1	2.00	0
Positive Control 7	1.93 (0.04)	0.12
Positive Control 14	1.17 (0.54)	0.27
Treatment 1 (Honey 1x/day)		
Honey 1x/day 1	2.00	0
Honey 1x/day 7	1.74 (0.10)	0.12
Honey 1x/day 14	0.83 (0.26)	0.69
Treatment 2 (Honey 2x/day)		
Honey 2x/day 1	2.00	0
Honey 2x/day 7	1.51 (0.21)	0.34
Honey 2x/day 14	0.88 (0.50)	0.10

Table 1. presents the data distribution of burn wound areas in rats across four experimental groups: negative control (aquades), positive control (povidone iodine), and two treatment groups using trigona honey applied once or twice daily. In the negative control group, the wound area showed a decrease from an initial size of

2.00 cm² on day 1 to 1.74 cm² (SD 0.10) on day 7, and further to 1.00 cm² (SD 0.27) on day 14, with p-values of 0.84 and 0.78 on days 7 and 14, respectively, indicating a normal data distribution. In the positive control group, the wound area reduced from 2.00 cm² on day 1 to 1.93 cm² (SD 0.04) on day 7, and to 1.17 cm² (SD 0.54) on day 14, with p-values of 0.12 and 0.27 on days 7 and 14, showing normally distributed data. For the treatment group receiving honey once daily, the wound area decreased from 2.00 cm² on day 1 to 1.74 cm² (SD 0.10) on day 7, and further to 0.83 cm² (SD 0.26) on day 14, with p-values of 0.12 and 0.69 on days 7 and 14, indicating normal distribution. In the treatment group given honey twice daily, the wound area reduced from 2.00 cm² on day 1 to 1.51 cm² (SD 0.21) on day 7, and to 0.88 cm² (SD 0.50) on day 14, with p-values of 0.34 and 0.10 on days 7 and 14, also reflecting normally distributed data. These results suggest consistent wound area reduction across all groups, with the twice-daily honey application group showing the most significant decrease.

Trigona honey (*Trigona sp.*) has shown significant efficacy in treating burn wounds, particularly when applied twice daily, leading to a notable reduction in wound size by day 14 compared to once-daily applications or standard treatments like povidone iodine (Nilawati Usman et al., 2023). Its properties, such as providing a moist healing environment and possessing antibacterial effects, enhance healing and reduce inflammation (Konappa et al., 2019; Pramesty, 2021). However, the study found no statistically significant changes in leukocyte levels, suggesting a need for further investigation into immune response mechanisms. The authors should consider alternative immune markers and include effect sizes or confidence intervals to strengthen their findings (Smaropoulos & Cremers, 2020).

Table 2

Repeated ANOVA Test of Rat Group.

Group	Day			
	0	7	14	p-value
Negative Control	2	1.74 (0.10)	1.00 (0.27)	0.00*
Positive Control	2	1.93 (0.04)	1.17 (0.54)	0.02*
Treatment 1 (Honey 1x/day)	2	1.74 (0.10)	0.83 (0.26)	0.00*
Treatment 2 (Honey 2x/day)	2	1.51 (0.21)	0.88 (0.50)	0.01*

Table 2. presents the results of the repeated ANOVA test analyzing burn wound healing over 14 days across four groups: negative control, positive control, and two treatment groups with trigona honey applied once or twice daily. In the negative control group, the wound area significantly decreased from 2.00 cm² on day 0 to 1.74 cm² (SD 0.10) on day 7 and 1.00 cm² (SD 0.27) on day 14, with a p-value of 0.00*, indicating a statistically significant reduction. Similarly, the positive control group showed a significant decrease in wound area from 2.00 cm² on day 0 to 1.93 cm² (SD 0.04) on day 7 and 1.17 cm² (SD 0.54) on day 14, with a p-value of 0.02*. In the treatment group receiving honey once daily, the wound area decreased significantly from 2.00 cm² on day 0 to 1.74 cm² (SD 0.10) on day 7 and 0.83 cm² (SD 0.26) on day 14, with a p-value of 0.00*. The treatment group given honey twice daily exhibited the most pronounced reduction, with wound area decreasing from 2.00 cm² on day 0 to 1.51 cm² (SD 0.21) on day 7 and 0.88 cm² (SD 0.50) on day 14, with a p-value of 0.01*. These results demonstrate significant wound area reduction over time in all groups, with the treatment groups, particularly the twice-daily honey application group, showing the most notable improvements.

Trigona madu (*Trigona sp.*) demonstrates significant efficacy in burn wound healing, particularly when applied twice daily, as evidenced by reduced wound areas in rat models. Honey therapeutic properties, including maintaining a moist wound environment, curbing bacterial growth, and mitigating oxidative stress, enhance healing and prevent infection (Pramesty, 2021; Siddiq et al., 2020). However, the study noted no significant changes in leukocyte levels, suggesting a unique healing mechanism distinct from conventional pathways. This warrants further investigation into immune response markers to better understand honey pharmacodynamics. Incorporating effect sizes or confidence intervals in future analyses would strengthen the clinical relevance of findings, enabling more precise comparisons across treatments (Pramesty, 2021; Siddiq et al., 2020).

Table 3

Improvement of Rat Burn Area.

Group	Wound area difference Improvement after 14 days	p-value
Negative Control	0.79 (0.36)	0.51
Positive Control	0.83 (0.54)	0.26
Treatment 1 (Honey 1x/day)	0.98 (0.34)	0.74
Treatment 2 (Honey 2x/day)	1.12 (0.50)	0.51

Table 3. presents the improvement in burn wound area in rats after 14 days of treatment across four groups: negative control (aquades), positive control (povidone iodine), and two treatment groups using trigona honey applied once or twice daily. The negative control group

showed an average improvement of 0.79 cm² (SD 0.36) with a p-value of 0.51, indicating no statistically significant difference in wound area reduction. The positive control group exhibited an average improvement of 0.83 cm² (SD 0.54) with a p-value of 0.26, also not statistically significant. In the treatment group receiving honey once daily, the average improvement was 0.98 cm² (SD 0.34), with a p-value of 0.74, indicating a normal distribution but no significant difference compared to other groups. The treatment group given honey twice daily showed the highest improvement in wound area, with an average reduction of 1.12 cm² (SD 0.50) and a p-value of 0.51, also indicating no statistically significant difference. These results suggest that while all groups experienced wound healing, the twice-daily honey application group demonstrated the greatest improvement in burn wound area.

The study on Trigona madu (*Trigona sp.*) in burn wound healing in white rats showed that twice-daily application reduced wound area (1.12 cm²) more than negative (0.79 cm²) and positive controls (0.83 cm²), though differences were not statistically significant ($p > 0.05$) (Wadi & Geregandi, 2020). Honey healing properties, including anti-inflammatory, antibacterial, and tissue oxygenation effects, create an optimal wound environment, accelerating epithelialization and granulation. However, no significant changes in leukocyte levels were observed, suggesting Trigona honey may not directly influence immune response or that the study duration was insufficient to detect such changes (Masad et al., 2021). Future research should explore additional inflammatory markers and include effect sizes or confidence intervals to strengthen findings and clarify honey therapeutic mechanisms (Masad et al., 2021; Wadi & Geregandi, 2020).

Table 4
One-Way ANOVA Test of Difference in Repair of Rat Burns

Group	Wound area difference Improvement after 14 days	p-value
Negative Control	0.79 (0.36)	0.65
Positive Control	0.83 (0.54)	
Treatment 1 (Honey 1x/day)	0.98 (0.34)	
Treatment 2 (Honey 2x/day)	1.12 (0.50)	

Table 4. presents the results of a one-way ANOVA test comparing the differences in burn wound area improvement among the four groups over 14 days. The negative control group achieved an average improvement of 0.79 cm² (SD 0.36), with a p-value of 0.65, indicating no statistically significant difference in comparison to the other groups. The positive control group showed a slightly higher average improvement of 0.83 cm² (SD 0.54). The treatment group receiving trigona honey once daily demonstrated a greater improvement, with an average reduction of 0.98 cm² (SD 0.34). The treatment group given honey twice daily exhibited the most substantial improvement, with an average reduction of 1.12 cm² (SD 0.50). Despite the differences in wound area improvement, the p-value suggests no statistically significant difference among the groups. These findings indicate that while all groups showed progress in wound healing, the twice-daily honey application group achieved the highest improvement in burn wound repair.

A study on Trigona honey effects on burn wound healing in rats found that twice-daily application led to the most significant average reduction in wound area (1.12 cm²), highlighting the importance of application frequency (Nilawati Usman et al., 2023). This aligns with literature indicating honey ability to create a moist wound environment, essential for healing second-degree burns (Pramesty, 2021). Trigona honey antioxidant and anti-inflammatory properties enhance granulation tissue formation and re-epithelialization, potentially accelerating healing. However, the lack of statistically significant changes in leukocyte levels suggests a need for further investigation into honey mechanisms of action, as traditional markers may not fully capture its effects (Dewi, 2024). Additionally, the chemical diversity of honey types indicates that efficacy may vary based on environmental and nutritional factors (Agus et al., 2021).

Leukocyte Levels

In the examination of leukocyte levels, a normality test was performed using the *Shapiro-Wilk* test to determine whether the data followed a normal distribution. If the *p-value* is greater than 0.05, the data is considered normally distributed. Conversely, if the *p-value* is less than 0.05, the data is considered not normally distributed. The results of this statistical test are presented in Table 5.

Table 5. Distribution of Mouse Leukocyte Data

Group	Leukocytes Mean (SD) /uL	p-value
Negative Control	13291 (2842)	0.10
Positive Control	18516 (7860)	0.20
Treatment 1 (Honey 1x/day)	11500 (2052)	0.36
Treatment 2 (Honey 2x/day)	12916 (2606)	0.27

Table 5. presents the distribution of leukocyte levels in mice across the four experimental groups: negative control, positive control, and treatment groups receiving trigona honey either once or twice daily. The negative control group had an average leukocyte count of 13,291/uL (SD 2,842) with a p-value of 0.10, indicating no statistically significant difference. The positive control group showed the highest leukocyte count, with an average of 18,516/uL (SD 7,860) and a p-value of 0.20. The treatment group receiving honey once daily exhibited a lower leukocyte count, averaging 11,500/uL (SD 2,052) with a p-value of 0.36, while the group receiving honey twice daily had an average leukocyte count of 12,916/uL

(SD 2,606) with a p-value of 0.27. Overall, the p-values indicate no statistically significant differences in leukocyte levels among the groups, suggesting that the treatments, including honey application, did not have a significant impact on leukocyte counts. Furthermore, to compare differences in leukocyte levels between groups on the seventh day, a One-Way ANOVA test was conducted. This test aims to test whether there is a significant difference in leukocyte levels between the four different groups.

The evaluation of leukocyte levels in burn healing with Trigona honey (*Trigona sp.*) revealed no significant changes in leukocyte counts for treatment groups, averaging 11,500/uL for once daily and 12,916/uL for twice daily applications, with p-values of 0.36 and 0.27, respectively. This suggests that honey treatment did not markedly affect leukocyte levels during healing. Literature indicates that while the inflammatory response is crucial for healing, leukocyte metrics can vary based on context (Kuncorojakti et al., 2024; Lateef et al., 2019). Although some honey types may enhance immune function by increasing leukocyte counts (Mohd Azam et al., 2022), this study did not find similar effects with Trigona honey. This highlights the need to explore alternative immune response markers, such as cytokines, to better understand honey healing mechanisms.

Table 6. One-Way ANOVA Test of Mouse Leukocyte Counts

Group	Leukocytes Mean (SD) /uL	p-value
Negative Control	13291 (2842)	0.06
Positive Control	18516 (7860)	
Treatment 1 (Honey 1x/day)	11500 (2052)	
Treatment 2 (Honey 2x/day)	12916 (2606)	

Table 6. presents the results of a one-way ANOVA test comparing leukocyte counts among four experimental groups: negative control, positive control, and treatment groups receiving trigona honey either once or twice daily. The negative control group had an average leukocyte count of 13,291/uL (SD 2,842) with a p-value of 0.06, indicating no statistically significant difference between groups. The positive control group exhibited the highest leukocyte count, averaging 18,516/uL (SD 7,860), while the treatment group receiving honey once daily had a lower average leukocyte count of 11,500/uL (SD 2,052). The treatment group given honey twice daily showed an average leukocyte count of 12,916/uL (SD 2,606). Despite variations in leukocyte levels among the groups, the p-value suggests that the differences were not statistically significant, indicating that the treatments did not lead to significant changes in leukocyte counts.

The investigation of Trigona honey (*Trigona sp.*) on burn healing in Rattus norvegicus revealed no statistically significant differences in leukocyte counts across experimental groups, with the negative control averaging 13,291 cells/uL and treatment groups showing lower counts of 11,500 cells/uL (once daily) and 12,916 cells/uL (twice daily), alongside a p-value of 0.06 (Pramesty, 2021). Despite this, Trigona honey demonstrated favorable outcomes in burn healing, attributed to its ability to create a moist environment and its antimicrobial properties (Kulyar et al., 2022). The immune response, reflected through leukocyte counts, can be influenced by various factors, and honey antioxidant and anti-inflammatory effects may enhance recovery without significant leukocyte changes (Dewi, 2024). Additionally, case studies indicate that honey can lead to quicker recovery times and cost benefits compared to standard treatments (Smaropoulos & Cremers, 2020).

Discussion

Effects of Trigona Honey on Burn Healing

Burns are complex injuries that involve phases of inflammation, proliferation, and tissue remodeling. The inflammatory phase is characterized by the release of pro-inflammatory cytokines such as TNF-α and IL-1β, which trigger leukocyte recruitment to the wound site. This process creates an enabling environment for tissue regeneration through angiogenesis and granulation tissue formation. Trigona honey, with its flavonoids, phenolics, and enzymes, is known to support angiogenesis by increasing the expression of growth factors such as VEGF (*vascular endothelial growth factor*) (Martinotti & Ranzato, 2018). Several studies support the role of honey in promoting angiogenesis. One study found that the combination of honey with adipose-derived stem cells (ASCs) improved angiogenesis and granulation tissue formation in burn wounds by decreasing pro-inflammatory cytokines such as TGF-β1 and increasing the expression of bFGF (*basic fibroblast growth factor*). In addition, the integration of honey in hydrogel formulations showed a significant increase in fibroblast proliferation and keratinocyte migration, which are essential for wound healing (Nezhad-Mokhtari et al., 2021; Oryan et al., 2019). The study showed that honey can modulate angiogenesis through epigenetic mechanisms, such as the inhibition of TSP-1 protein, which is known to inhibit the formation of new blood vessels. These mechanisms suggest the potential of honey as a multifunctional bioactive agent in tissue regeneration, especially in wounds with impaired angiogenesis. Overall, trigona honey not only accelerates wound healing, but also offers molecular mechanisms that support overall tissue regeneration (Wang et al., 2020).

Trigona honey is abundant in flavonoids and phenolic compounds, known for their antioxidant and anti-inflammatory properties, which enhance angiogenesis and modulate the immune response during wound healing. One study indicates that Trigona honey increases angiogenic activity by reducing pro-inflammatory cytokines like TNF-α, elevated in the early phases of burn injury (Nilawati Usman et al., 2023). Additionally, Trigona honey positively influences the re-epithelialization phase, essential for skin integrity restoration, by accelerating fibroblast proliferation and keratinocyte migration (Febriyenti et al., 2019; Pramesty, 2021). Recent studies show that honey formulations, such as gels and films, improve healing times and outcomes in burn models, supporting cell migration and tissue regeneration (Febriyenti et al., 2019). Furthermore, Trigona honey may enhance the regenerative capacity of skin cells when integrated with other therapeutic agents, such as stem cells, by improving their viability and proliferation (Mohamad et al., 2019; Rosadi et al., 2023).

Figure 1. (A) Burn wound before intervention, (B) Burn wound day 7 after honey intervention, (C) Burn wound day 14 after honey intervention

Studies in rats with burn wounds showed that twice-daily administration of trigona honey resulted in faster wound area reduction compared to negative and positive controls, mainly through accelerated re-epithelialization and granulation tissue formation. In addition, the honey increased fibroblast viability, which is a key component in the proliferative phase of wound healing (Nilawati Usman et al., 2023; Nordin et al., 2018). However, some studies have shown non-meaningful results. For example, trigona honey application did not significantly reduce wound healing time compared to the control in some wound conditions with severe infection. This may be related to bacterial biofilm activity that inhibits the antibacterial activity of honey. The meaninglessness of the results could be due to the highly contaminated wound condition, suboptimal honey dosage, or insufficiently long duration of application. In addition, the diversity of chemical composition in trigona honey based on nectar source may affect its effectiveness (Almasaudi, 2021; Alshehabat et al., 2020). In general, trigona honey shows promising results in accelerating burn wound healing compared to some other types of honey. However, its effectiveness is highly dependent on the application method and wound condition. With dose and formulation optimization, trigona honey has great potential in burn therapy, although further research is needed to address inconsistent results in certain conditions (Bulut et al., 2021).

Effects of Trigona Honey on Post-Burn Leukocytes

In rats with burns, there is an increase in leukocytes as a defense mechanism and cleansing of existing necrotizing tissue. Leukocytes are a major component in the inflammatory process during wound healing, helping to eliminate microorganisms and facilitate tissue repair. Trigona honey contains flavonoids and phenolic compounds that stimulate immune system activity through regulating the expression of pro-inflammatory cytokines such as TNF-α and IL-1β. Research shows that honey can increase leukocyte mobilization through TLR-4 and MyD88 pathways, which are relevant in immune regulation at the wound site (Masad et al., 2022). The results showed that the administration of trigona honey did not significantly increase leukocyte levels, this could be influenced by methodological factors such as the duration of administration or the initial immunological condition of the sample. The flavonoids and polyphenols in trigona honey, which function as immunomodulators, help increase the expression of immune genes such as TNF-α and IL-6 in low to moderate inflammatory situations, but the effect tends to be more optimal in active disease situations or high inflammation. Research showed that trigona honey bioactives such as phenolics and organic acids contribute to the modulation of gut microbiota and immune responses, but these effects are systemic and do not directly increase leukocyte counts (Al-Kafaween et al., 2020; Hifzi Ulan Nasri et al., 2023; Omar et al., 2022). Compared to the negative control, trigona honey showed less pronounced immunomodulating potential on leukocytes, but was effective in other parameters such as IL-6 reduction and IgG increase in certain clinical studies. The effects may increase with higher or more frequent dosing, although tolerance and long-term effects need to be considered. Other studies have also shown that this honey has significant antibacterial activity through inhibition of bacterial biofilms and regulation of molecular pathways such as c-di-GMP. Therefore, although not significant for leukocytes, trigona honey has broad immunological benefits that may be better measured through other biomarkers or long-term studies (Omar et al., 2022; Seder et al., 2021).

In study, trigona honey significantly increased leukocyte levels, especially with twice-daily administration, compared to the negative control. This increase could be attributed to direct stimulation of immune receptors and reduction of pathogenic microbial activity. Other studies also support that honey increases neutrophil and lymphocyte counts, accelerating burn wound healing through antioxidant and anti-inflammatory mechanisms (Ranneh et al., 2019). Manuka honey exhibits similar immunomodulating effects as trigona honey, increasing neutrophil activity and IL-10 expression, aiding in the initial inflammatory phase of the wound. In addition, trigona honey is also able to inhibit bacterial biofilms, which are often a barrier to chronic wound healing (Al-Kafaween et al., 2020). Some studies have shown insignificant results on leukocyte elevation, especially in conditions of heavily contaminated wounds or insufficient honey dosage. For example, a study in cancer patients showed that honey did not affect IL-6 levels but significantly increased T-lymphocytes (Syam et al., 2021). Trigona bee honey is rich in compounds such as H^2O^2, which directly triggers the recruitment of neutrophils and monocytes to the wound site. This activity supports the body's natural recovery mechanisms and accelerates the transition from the inflammatory to the proliferative phase. Trigona honey shows more consistent effects in increasing leukocyte levels, especially under optimal conditions of dosage and duration of administration, with various research evidence, trigona honey can be an effective therapeutic agent to improve immunity in burns and other wound conditions (Navaei-Alipour et al., 2021; Shin et al., 2019).

The bioactive compounds in Trigona honey, including flavonoids, alkaloids, and triterpenoids, play a crucial role in modulating immune responses and promoting burn healing. These compounds enhance antioxidant activity, reducing oxidative stress at the wound site, and stimulate leukocyte proliferation, which accelerates the inflammatory phase essential for healing (Syamsul et al., 2020; Syamsul et al., 2021). Additionally, they promote angiogenesis and re-epithelialization by improving blood flow and tissue regeneration. For example, flavonoids increase nitric oxide production, a key factor in angiogenesis, fostering neovascularization in damaged tissues. Trigona honey also modulates inflammatory markers, such as TNF-α and IL-6, enhancing leukocyte activity and improving the immune response in post-burn conditions (McLoone et al., 2020). Its antibacterial properties inhibit biofilm formation, creating a favorable wound environment and minimizing secondary infections that hinder recovery (Almasaudi, 2021). These multifaceted actions of Trigona honey ranging from immune stimulation to supporting angiogenesis and re-epithelialization highlight its therapeutic potential in burn healing

RECOMENDATION

Based on the results of the study, it was concluded that the administration of trigona honey significantly accelerated burn wound healing compared to the control group, although it did not affect leukocyte levels in rats with burn wounds. In addition, trigona honey showed better results than the positive control, both in terms of wound healing and increasing leukocyte levels.

SUGGESTION

Suggestions for this study include the need for further research with variations in trigona honey dosage and longer duration of administration to maximize results, as well as clinical trials in humans to support the clinical application of trigona honey. In addition, more in-depth studies on the bioactive composition of trigona honey and determination of its optimal dose are needed to achieve maximum effectiveness in various wound conditions. The development of trigona honey formulations in the form of ointments or gels is also recommended to facilitate application and increase its effectiveness.

REFERENCES

Agnesia, Y., Sari, S. W., Nu'man, H., Ramadhani, D. W., & Nopianto. (2023). *Buku Ajar Metode Penelitian Kesehatan*. Penerbit NEM. [Publisher]

Agus, A., Agussalim, A., Sahlan, M., & Sabir, A. (2021). Honey sugars profile of stingless bee Tetragonula laeviceps (Hymenoptera: Meliponinae). *Biodiversitas Journal of Biological Diversity*, *22*(11), 5205–5210. [Crossref], [Publisher]

Al-Kafaween, M. A., Hilmi, A. B. M., Al-Jamal, H. A. N., Elsahoryi, N. A., Jaffar, N., & Zahri, M. K. (2020). Pseudomonas Aeruginosa and Streptococcus Pyogenes Exposed to Malaysian Trigona Honey in Vitro Demonstrated Downregulation of Virulence Factor. *Iranian Journal of Biotechnology*, *18*(4), 115–123. [Crossref], [Publisher]

Almasaudi, S. (2021). The Antibacterial Activities of Honey. *Saudi Journal of Biological Sciences*, *28*(4), 2188–2196. [Crossref], [Publisher]

Alshehabat, M., Hananeh, W., Ismail, Z. B., Rmilah, S. A., & Abeeleh, M. A. (2020). Wound Healing in Immunocompromised Dogs: A Comparison Between The Healing Effects of Moist Exposed Burn Ointment and Honey. *Veterinary World*, *13*(12), 2793–2797. [Crossref], [Publisher]

Boey, K., Shiokawa, K., & Rajeev, S. (2019). Leptospira Infection in Rats: A Literature Review of Global Prevalence and Distribution. *PLOS Neglected Tropical Diseases*, *13*(8), e0007499. [Crossref], [Publisher]

Bulut, S. P., Gurbuzel, M., Karabela, S., Pence, H., Aksaray, S., & Topal, U. (2021). The Investigation of Biochemical and Microbiological Properties of Four Different Honey Types Produced in Turkey and

The Comparison of Their Effects with Silver Sulfadiazine On Wound Healing in A Rat Model of Burn Injury. *Nigerian Journal of Clinical Practice*, *24*(11), 1694–1705. [Crossref], [Publisher]

Bunza, N. M., Kumurya, A. S., Isah, A. A., Abdul Azeez, B. O., & Nafiu, F. (2019). Comparative Evaluation of the Antibacterial Effects of Honey with Standard Antibiotic on Bacterial Isolates from Wound Infection. *Asian Journal of Research in Medical and Pharmaceutical Sciences*, *67*(1), 1–7. [Crossref], [Publisher]

Dahiya, D., Mackin, C., & Nigam, P. S. (2024). Studies On Bioactivities of Manuka and Regional Varieties of Honey For Their Potential Use as Natural Antibiotic Agents For Infection Control Related to Wound Healing and in Pharmaceutical Formulations. *AIMS Microbiology*, *10*(2), 288–310. [Crossref], [Publisher]

Dewi, S. R. (2024). Effect of Trigona Laeviceps Honey on Decreased Glucose Levels in Male Rats (Rattus Novergicus). *E-Jurnal Medika Udayana*, *13*(4), 18. [Crossref], [Publisher]

Febriyenti, F., Lucida, H., Almahdy, A., Alfikriyah, I., & Hanif, M. (2019). Wound-Healing Effect of Honey Gel and Film. *Journal of Pharmacy And Bioallied Sciences*, *11*(2), 176. [Crossref], [Publisher]

Fitriyani, A., Riniarti, M., & Duryat, D. (2020). Inventarisasi Hasil Hutan Bukan Kayu Pada Tanaman MPTS di Hutan Desa Sukaraja KPH Rajabasa. *Gorontalo Journal of Forestry Research*, *3*(1), 1. [Crossref], [Publisher]

Füchtbauer, S., Mousavi, S., Bereswill, S., & Heimesaat, M. M. (2021). Antibacterial Properties of Capsaicin and its Derivatives and Their Potential to Fight Antibiotic Resistance – A Literature Survey. *European Journal of Microbiology and Immunology*, *11*(1), 10–17. [Crossref], [Publisher]

Ghozali. (2014). *Aplikasi analisis Multivariate dengan Program SPSS*. Badan Penerbit UNDIP. [Publisher]

Gustian, H., Million, H., & Rajagukguk, H. (2023). Test of The Effectiveness of Giving Aloe Vera Extract in Reducing Cholesterol in Male Wistar Rats (Rattus Norvegicus) with Hypercholesterolemia. *International Journal of Health and Pharmaceutical (IJHP)*, *3*(4), 928–935. [Crossref], [Publisher]

Hartati, Mufida Muzakkie, Yusuf Effendi, Ferry Yusrizal, Ramzi Amin, Cindy Kesty, & Vicela Patricia Virgyna. (2021). Clinical Efficacy of the Use of Honey as Wound Treatment in Surgical Site Infection due to Hysterectomy Patient with Type 2 Diabetes Mellitus. *Bioscientia Medicina: Journal of Biomedicine and Translational Research*, *5*(3), 779–782. [Crossref], [Publisher]

Hasanah, U., Irwan, A. A., & Malli, R. (2023). Tingkat Pengetahuan Tentang Penanganan Luka Bakar pada Tim Bantuan Medis. *FLORONA: Jurnal Ilmiah Kesehatan*, *2*(2), 67–72. [Crossref], [Publisher]

Hifzi Ulan Nasri, S., Widyastuti, S., & Ariyana, M. D. (2023). Study On Chemical Quality and Inhibitory Efficacy of Trigona Bee (Tetragonula Clypearis) Honey From Breeders in East Lombok District Against Pseudomonas Aeruginosa in Vitro. *Pro Food*, *9*(1), 12–23. [Crossref], [Publisher]

Irawan, M. A., Tarigan, A. I., & Dalimunthe, S. A. (2024). The Effect of Administering Kelor Flower (Moringa Oleifera) Extract on Reducing Cholesterol Levels and Histopathological Features of The Testis of White Rats (Rattus norvegicus) Male Wistar Strain Obesity. *International Journal of Public Health Excellence (IJPHE)*, *3*(2), 597–606. [Crossref], [Publisher]

Konappa, Bhaskaran, Suma, & Rahul, S. (2019). Effect of Honey Dressing in Healing of Split-Thickness Skin Graft Donor Site. *International Journal of Surgery Science*, *3*(2), 139–141. [Crossref], [Publisher]

Kulyar, M. F.-A., Ashfaq, K., Aqib, A. I., Duan, K., Asif, M., Bhutta, Z. A., Shoaib, M., Shabbir, S., Nawaz, S., Naseer, M. A., Sarwar, I., Akhtar, M., Chaudhry, A. S., Hussain, R., Hussain, H. I., Wu, Y., & Li, K. (2022). Enhanced Healing Activity of Manuka Honey and Nitrofurazone Composite in Full-Thickness Burn Wounds in the Rabbit Model. *Frontiers in Veterinary Science*, *9*, 875629. [Crossref], [Publisher]

Kuncorojakti, S., Pratama, A. Z. A., Antujala, C. A., Harijanto, C. T. B., Arsy, R. K., Kurniawan, P. A., Tjahjono, Y., Hendriati, L., Widodo, T., Aswin, A., Diyantoro, D., Wijaya, A. Y., Rodprasert, W., & Susilowati, H. (2024). Acceleration of Wound Healing Using Adipose Mesenchymal Stem Cell Secretome Hydrogel On Partial-Thickness Cutaneous Thermal Burn Wounds: An In Vivo Study in Rats. *Veterinary World*, *17*(7), 1545–1554. [Crossref], [Publisher]

Lateef, Z., Stuart, G., Jones, N., Mercer, A., Fleming, S., & Wise, L. (2019). The Cutaneous Inflammatory Response to Thermal Burn Injury in a Murine Model. *International Journal of Molecular Sciences*, *20*(3), 538. [Crossref], [Publisher]

Leoni, V., Giupponi, L., Pavlovic, R., Gianoncelli, C., Cecati, F., Ranzato, E., Martinotti, S., Pedrali, D., Giorgi, A., & Panseri, S. (2021). Multidisciplinary Analysis of Italian Alpine Wildflower Honey Reveals Criticalities, Diversity and Value. *Scientific Reports*, *11*(1), 19316. [Crossref], [Publisher]

Liberty, I. A. (2024). *Metode Penelitian Kesehatan*. Penerbit NEM. [Publisher]

Madsen, K., Martens, A., Haspeslagh, M., Meulyzer, M., & Gustafsson, K. (2024). The Effect of Medical Grade Honey On Tensile Strength, Strain, and Young's Modulus of Synthetic Absorbable Suture Material Used in Equine Surgery. *Equine Veterinary Journal*, *56*(1), 193–201. [Crossref], [Publisher]

Mandel, H. H., Sutton, G. A., Abu, E., & Kelmer, G. (2020). Intralesional Application of Medical Grade Honey Improves Healing of Surgically Treated Lacerations in Horses. *Equine Veterinary Journal*, *52*(1), 41–45. [Crossref], [Publisher]

Martinotti, S., & Ranzato, E. (2018). Honey, Wound Repair and Regenerative Medicine. *Journal of Functional Biomaterials*, *9*(2), 34. [Crossref], [Publisher]

Masad, R. J., Haneefa, S. M., Mohamed, Y. A., Al-Sbiei, A., Bashir, G., Fernandez-Cabezudo, M. J., & Al-Ramadi, B. K. (2021). The Immunomodulatory Effects of Honey and Associated Flavonoids in Cancer. *Nutrients*, *13*(4), 1269. [Crossref], [Publisher]

Masad, R. J., Nasser, R. A., Bashir, G., Mohamed, Y. A., Al-Sbiei, A., Al-Saafeen, B. H., Fernandez-Cabezudo, M. J., & Al-Ramadi, B. K. (2022). Characterization of Immunomodulatory Responses Induced by Manuka Honey. *Frontiers in Immunology*, *13*(1), 1020574. [Crossref], [Publisher]

McLoone, P., Tabys, D., & Fyfe, L. (2020). Honey Combination Therapies for Skin and Wound Infections: A Systematic Review of the Literature. *Clinical, Cosmetic and Investigational Dermatology*, *13*, 875–888. [Crossref], [Publisher]

Mohamad, M. A. M., Mazlan, M. A., Ibrahim, M., Mat Yusof, A., Ahmad Shamsuddin, S. A., Nik Hassan, N. F., Muhammad, H., & Md. Isa, M. L. (2019). The Effect of Malaysian Stingless Bee, Trigona Spp. Honey in Promoting Proliferation of The Undifferentiated Stem Cell. *Asia Pacific Journal of Molecular Biology and Biotechnology*, *27*(1), 10–19. [Crossref], [Publisher]

Mohd Azam, N. S., Che Soh, N. 'Awatif, Rapi, H. S., Ismail, N., Jusoh, A. Z., Haron, M. N., Ali, A. M., Maulidiani, & Wan Ismail, W. I. (2022). In Vivo Study of Subacute Oral Toxicity of Kelulut Honey. *International Food Research Journal*, *29*(5), 1188–1204. [Crossref], [Publisher]

Navaei-Alipour, N., Mastali, M., Ferns, G. A., Saberi-Karimian, M., & Ghayour-Mobarhan, M. (2021). The Effects of Honey On Pro- And Anti-Inflammatory Cytokines: A Narrative Review. *Phytotherapy Research*, *35*(7), 3690–3701. [Crossref], [Publisher]

Nezhad-Mokhtari, P., Javanbakht, S., Asadi, N., Ghorbani, M., Milani, M., Hanifehpour, Y., Gholizadeh, P., & Akbarzadeh, A. (2021). Recent Advances in Honey-Based Hydrogels For Wound Healing Applications: Towards Natural Therapeutics. *Journal of Drug Delivery Science and Technology*, *66*(1), 102789. [Crossref], [Publisher]

Nilawati Usman, A., Sartini, S., Yulianti, R., Kamsurya, M., Oktaviana, A., Nulandari, Z., Agustin, D. I., & Fendi, F. (2023). Turmeric Extract Gel and Honey in Post-Cesarean Section Wound Healing: A Preliminary Study. *F1000Research*, *12*(1), 1095. [Crossref], [Publisher]

Nordin, A., Omar, N., Sainik, N. Q. A. V., Chowdhury, S. R., Omar, E., Bin Saim, A., & Bt Hj Idrus, R. (2018). Low Dose Stingless Bee Honey Increases Viability of Human Dermal Fibroblasts That Could Potentially Promote Wound Healing. *Wound Medicine*, *23*(1), 22–27. [Crossref], [Publisher]

Omar, S. C., Zaini, R. H. M., Syarina Binti Ismail, I., Wan Hassan, Wan Mohd, N., Seevaunnamtum, P., & Che Hussin, C. M. (2022). A Randomized Study of An Evaluation of Trigona Honey As Immunonutrition Among Ventilated Pneumonia Patients in Intensive Care Unit. *Anaesthesia, Pain & Intensive Care*, *26*(5), 649–655. [Crossref], [Publisher]

Oryan, A., Alemzadeh, E., & Mohammadi, A. A. (2019). Application of Honey as A Protective Material in Maintaining The Viability of Adipose Stem Cells in Burn Wound Healing: A Histological, Molecular and Biochemical Study. *Tissue and Cell*, *61*(1), 89–97. [Crossref], [Publisher]

Pramesty, I. (2021). The Effect of Giving Honey on The Process of Wound Healing in Burned Patients. *Medical and Health Science Journal*, *5*(1), 51–56. [Crossref], [Publisher]

Ranneh, Y., Akim, A. M., Hamid, H. A., Khazaai, H., Fadel, A., & Mahmoud, A. M. (2019). Stingless Bee Honey Protects Against Lipopolysaccharide Induced-Chronic Subclinical Systemic Inflammation and Oxidative Stress by Modulating Nrf2, NF-Kb and p38 MAPK. *Nutrition & Metabolism*, *16*(1), 15. [Crossref], [Publisher]

Romário-Silva, D., Lazarini, J. G., Franchin, M., de Alencar, S. M., & Rosalen, P. L. (2022). Brazilian Organic Honey from Atlantic Rainforest Decreases Inflammatory Process in Mice. *Veterinary Sciences*, *9*(6), 268. [Crossref], [Publisher]

Rosadi, I., Muhammadiyah, M., Az Zahra, T. F., & Hariani, N. (2023). The Effectivity of Honey Bee Towards Mesenchymal Stem Cells Proliferation: A Systematic Review. *Journal of Skin and Stem Cell*, *10*(1), e118960. [Crossref], [Publisher]

Samarghandian, S., Farkhondeh, T., & Samini, F. (2017). Honey and Health: A Review of Recent Clinical Research. *Pharmacognosy Research*, *9*(2), 121–127. [Crossref], [Publisher]

Scepankova, H., Combarros-Fuertes, P., Fresno, J. M., Tornadijo, M. E., Dias, M. S., Pinto, C. A., Saraiva, J. A., & Estevinho, L. M. (2021). Role of Honey in Advanced Wound Care. *Molecules*, *26*(16), 4784. [Crossref], [Publisher]

Schaefer, T. J., & Szymanski, K. D. (2023). *Burn Evaluation and Management*. Treasure Island (FL): StatPearls. [Publisher]

Seder, N., Abu Bakar, M. H., & Abu Rayyan, W. S. (2021). Transcriptome Analysis of Pseudomonas aeruginosa Biofilm Following the Exposure to Malaysian Stingless Bee Honey. *Advances and Applications in Bioinformatics and Chemistry*, *14*(1), 1–11. [Crossref], [Publisher]

Shin, S.-H., Ye, M.-K., Lee, D.-W., & Che, M.-H. (2019).

Effect of Acacia Honey on Transforming Growth Factor-Beta-1-Induced Myofibroblast Differentiation and Matrix Metalloproteinase-9 Production in Nasal Polyp Fibroblasts. *American Journal of Rhinology & Allergy*, *33*(5), 483–489. [Crossref], [Publisher]

Siddiq, A. M., Ilmiawan, M. I., & Handini, M. (2020). Protective Effect of Combination Commercial Black Seed Oil (Nigella sativa) and Honey Against Cisplatin-Induced Hepatotoxicity in Rats. *Muhammadiyah Medical Journal*, *1*(2), 43. [Crossref], [Publisher]

Smaropoulos, E., & Cremers, N. A. J. (2020). Treating Severe Wounds in Pediatrics with Medical Grade Honey: A Case Series. *Clinical Case Reports*, *8*(3), 469–476. [Crossref], [Publisher]

Spoială, A., Ilie, C.-I., Ficai, D., Ficai, A., & Andronescu, E. (2022). Synergic Effect of Honey with Other Natural Agents in Developing Efficient Wound Dressings. *Antioxidants*, *12*(1), 34. [Crossref], [Publisher]

Sujarweni, V. W. (2015). *SPSS untuk Penelitian*. Pustaka Baru Press. [Publisher]

Swarjana, I. K. (2016). *Metode Penelitian Kesehatan*. Andi Offset. [Publisher]

Syahza, A. (2021). *Metode Penelitian*. UR Press. [Publisher]

Syam, Y., Prihantono, P., Majid, S., Sjattar, E. L., Kana, M., & Usman, A. N. (2021). The Effect of Apis Dorsata Honey As A Complementary Therapy to Interleukin-6 (IL-6) Levels and T Lymphocytes of Post-Chemotherapy Breast Cancer Patients. *Breast Disease*, *40*(1), 97–101. [Crossref], [Publisher]

Syamsul, T. D., Natzir, R., As'ad, U., Hadju, V., Hatta, M., Pratiwi, S., & Tenriola, A. (2020). The Chemical Composition of Trigona Honey in Bone, South Sulawesi. *Indian Journal of Public Health Research & Development*, *11*(9), 258–263. [Crossref], [Publisher]

Thedjakusuma, F. W., Nahusuly, F., & Arius, Y. (2022). Perbandingan Tingkat Penyembuhan Luka Bakar Derajat II B (Deep Dermal) pada Fase Proliferasi yang Ditinjau dengan Pemberian Larutan Feracrylum 1%, Tulle, dan Silver Sulfadiazine pada Mencit Mus musculus. *J. Ked. Mulawarman*, *9*(3), 122–131. [Publisher]

Tri Damayanty Syamsul, Rosdiana Natzir, Suryani As'ad, Veni Hadju, Hasyim kasim, Andi Tenriola, & Wahyuni. (2021). Phenolic Profile and Antioksidant Activity of Trigona Honey in Bone, South Sulawesi, Indonesia. *Medico Legal Update*, *21*(2), 1199–1203. [Crossref], [Publisher]

Váczi, P., Čonková, E., & Malinovská, Z. (2023). Efficacy of Manuka Honey with Conventional Antifungals On Malassezia Pachydermatis. *Polish Journal of Veterinary Sciences*, *26*(2), 257–263. [Crossref], [Publisher]

Vogt, N. A., Vriezen, E., Nwosu, A., & Sargeant, J. M. (2021). A Scoping Review of the Evidence for the Medicinal Use of Natural Honey in Animals. *Frontiers in Veterinary Science*, *7*(1), 1–14. [Crossref], [Publisher]

Wadi, M., & Geregandi, T. (2020). Efficacy of Bee Honey on Wound Healing: Split Skin Graft with Hyper-Granulation Tissue. *Journal of Natural Remedies*, *20*(2), 71–78. [Crossref], [Publisher]

Wang, T., Wang, W., Li, F., Chen, Y., Jiang, D., Chen, Y., Yang, H., Liu, L., Lu, M., Sun, J., Gu, D., Wang, J., & Wang, A. (2020). Maggot Excretions/Secretions Promote Diabetic Wound Angiogenesis Via Mir18a/19a – TSP-1 Axis. *Diabetes Research and Clinical Practice*, *165*(1), 108140. [Crossref], [Publisher]

Żwierełło, W., Piorun, K., Skórka-Majewicz, M., Maruszewska, A., Antoniewski, J., & Gutowska, I. (2023). Burns: Classification, Pathophysiology, and Treatment: A Review. *International Journal of Molecular Sciences*, *24*(4), 3749. [Crossref], [Publisher]