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Research Article

Effectiveness of 70% Ethanol Extract of Pomegranate (*Punica granatum* Linn) Against the Healing Process of Incisions and Burns in Mice

Meilina Ratna Dianti*, Siti Maimunah

Faculty of Medicine and Health Science, UIN Maulana Malik Ibrahim, Malang, 65151, Indonesia

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***Corresponding author:**
Meilina Ratna Dianti
email:
meilina@farmasi.uin-malang.ac.id

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ABSTRACT

A wound is a traumatic occurrence that damages the skin's and subcutaneous tissue's continuity. For the treatment of skin wounds, it is normal practice in the medical community to administer analgesics, anti-inflammatories, antibiotics, and antiseptics. Anti-inflammatory, antibacterial, and antioxidant properties are required, as well as assistance for cell proliferation in the production of protein and collagen for the regeneration process. Pomegranate is frequently used as herbal medicine and is thought to heal various diseases and ailments, including burns. This investigation will assess the effects of 70% ethanol extract from pomegranate fruit on mouse incisions and second-degree burns. To assess the effect of the extract on the healing of cuts and burns in mice, wounds and second-degree burns were made and treated with a 70% ethanol extract of pomegranate at doses of 7%, 14%, and 28%. Administration of pomegranate fruit extract in 70% ethanol at the optimum dose of 28% was shown to considerably boost wound healing activity and this finding demonstrates the ability of pomegranate extract to treat wounds.

INTRODUCTION

A wound occurs when trauma causes damage to the skin's and subcutaneous tissue's continuity (Hertian *et al*., 2021; Sani *et al*., 2022). An incision wound, or simply an incision, is a trauma where the tissue is wounded by a sharp object (Fadhilah *et al*., 2022; Sani *et al*., 2022). Burns, on the other hand, are tissue losses or damage that occur when the surface of the body encounters heat, such as from hot water, fire, electricity, radiation, chemicals, or frost bites (Anggowarsito, 2014). These burns can harm or have an impact on many different body systems. Infections, hematomas, and hypertrophic tissue, also referred to as keloids, are a few problems from wounds brought on by inappropriate and hasty care (Ali, 2022). Burns can also cause systemic inflammatory response syndrome (SIRS), one of the clinical symptoms of inflammation. Sepsis, also known as septicemia, is a SIRS disease induced by a bacterial infection that, in extreme cases, can result in decreased cardiac output, tissue hypoperfusion, and multiple organ failures such as cardiac dysfunction, acute respiratory distress syndrome, and acute kidney failure (Farina *et al*., 2013; Purwanto and Astrawinata, 2018).

Treatment of skin wounds using analgesics, anti-inflammatories, antibiotics, and antiseptics is a common procedure in the medical field (Ramadhian and Widiastini, 2018). The process of healing a wound is intricate and all-encompassing. Anti-inflammatory, antibacterial, antioxidant, and anti-oxidative properties are necessary, as is support for cell proliferation in the production of protein and collagen for the regeneration process (Harris *et al*., 2020). Pomegranate (*Punica granatum* Linn) is frequently used as an herbal medicine and is said to be effective in treating a wide range of diseases and ailments. Diarrhea, dysentery, hemorrhoids, intestinal parasites, sore throats, diabetes, epistaxis, and vaginal itching have all been treated with pomegranate, which is also thought to be a heart tonic (Eghbali *et al*., 2021). Pomegranates have also been used to cure burns

and several illnesses, including diabetes, Alzheimer's disease, cancer, obesity, and cardiovascular problems (Almuhayawi *et al*., 2020; Faddladdeen and Ojaimi, 2019; Michicotl-Meneses *et al*., 2021; Moga *et al*., 2021; Wang *et al*., 2018; Zhang *et al*., 2022). Pomegranates contain high levels of polyphenols, including saponins, flavonoids, and hydrolyzed tannins (punicalin, pedunculagin, punikagin, gallic acid, and ellagic acid) (Celiksoy *et al*., 2020; Lukiswanto *et al*., 2019; Asadi *et al*., 2018). As a result, pomegranates have the potential to replace other treatments for open wounds.

Using plants as traditional medicine is one of the attempts being made to promote public health. Pharmaceuticals made from plants or from traditional medicine are unique in that their constituents are widely available in nature, have fewer adverse effects than chemical pharmaceuticals, and are also less expensive. Pomegranate is effective for treating open wounds because it is a potent antioxidant, anti-carcinogen, anti-inflammatory, and antibacterial. Accordingly, a study was conducted to determine the impact of pomegranate fruit extract in 70% ethanol on second-degree burns and wounds in mice.

METHODS

Plants Materials

Pomegranate fruit (*Punica granatum* Linn) obtained from Flora Gallery, Medokan Ayu Rungkut Surabaya and identified at UPT Materia Medica, Batu, East Java, Indonesia with key results of determination 074/601A/102.7/ 2020.

Chemical Materials

70% ethanol, 1% FeCl3 reagent, vanillin reagent, butanol, chloroform, acetic acid, TLC plate F254, NaNO2 reagent, 2N HCl, Emla 5% cream, Na-CMC, aquadest, and Bioplacenton obtained from the Nurra Gemilang store.

Mice

Mice (*Mus musculus*) strain Balb/c are the sample of this study. The inclusion criteria of the mice were: mice strain Balb/c; about 3-4 months old; body weight about 20-30 grams; and a healthy state characterized by active movement. Exclusion criteria from this sample were mice that died during treatment and mice that were anatomically deformed. The number of samples used was 40 based on calculations using the Federer formula. Sampling of experimental animals was chosen by simple random selection according to the inclusion criteria. Selected mice were included in the treatment group and adapted for 7 days.

Extraction

500 grams of pomegranate powder were utilized, and 1500 cc of 70% ethanol was employed in the maceration process for 72 hours in a closed jar with manual stirring. The soaked findings were filtered using filter paper and the filtrate and residue were separated after 72 hours. To create a thick pomegranate extract, the ethanol solvent was next evaporated using a rotary evaporator for 6 hours and then baked for 12 hours. The produced yield percentage is then determined. Calculations are made to determine the yield values of concentrated extracts.

Animal Test Preparation

In the Biomedical and Pharmacokinetics Laboratory, Department of Pharmacy, UIN Maulana Malik Ibrahim Malang, test animals were acclimated for seven days and daily provided with food and drink. The average for each treatment was then determined after weighing each mouse. In the initial round of treatment, mice had their back hair, which had a diameter of roughly 20 mm, shaved. Afterward, 70% alcohol was used to disinfect, and 5% Emla was used to numb the backs of the mice. Additionally, the mice's backs were burned in the form of second-degree burns using metal 10 mm in diameter that had been heated using an oven to 100% and attached for 5 seconds. Incisions were produced using a surgical blade/scalpel that was 1 cm long. The creation of water bubbles and the existence of a reddish hue on the mice's backs were indicators that second-degree burns had occurred.

The treatment group was split up into five groups: a positive control group, a negative control group, and three extract-based therapy groups. Each sort of wound is categorized into these five classes. Group 1 received therapeutic treatment with 7% of extract ethanol 70% pomegranate, Group 2 received therapeutic treatment with 14% extract ethanol 70% pomegranate, and Group 3 received therapeutic treatment with 28% extract ethanol 70% pomegranate both in burns and cuts. This variation in concentration was chosen to find out the highest level that can have an effect, where at doses smaller than the smallest, activity was found and the dose was increased to find out more. The positive control group received therapeutic treatment using Bioplacenton. The negative control group did not receive treatment.

Evaluation of Effectivity of Incisions and Burns

Evaluations of the wound's length and diameter and the degree of healing are the two forms of testing that are available. An evaluation of length and diameter was performed based on the standard of the inflammatory phase, which starts after the damage and lasts 4-5 days. The proliferative phase begins on the sixth day and lasts up to 2-3 weeks, the diameter of burns and wounds on the backs of mice were measured on days 2, 5, 8, 11 and 14 (Wijayantini *et al*., 2018). The Morton method is used for measurements, which are taken in four different directions and computed using the formula below:

1) The equation for calculating the incision's length:

$$px = \frac{px(1)+px(2)+px(3)+px(4)}{4}$$

Description: px = wound length on the x-th day (mm)

2) The equation for calculating a burn's diameter

$$dx = \frac{dx(1)+dx(2)+dx(3)+dx(4)}{4}$$

Description: dx = diameter of the wound on day x (mm)

Regarding the assessment of the healing percentage, On the fourteenth day, the percentage of burn healing was calculated. The following formula is then used to calculate it:

$$L = \frac{(D1)^2-(D2)^2}{(D1)^2} \times 100\%$$

Description:
L = Percentage of healing (%)
D1 = First day wound diameter (mm)
D2 = Diameter of the wound on the day of observation (mm)

Burn wound healing time was measured by giving therapy to mice that had been induced by burns according to the therapy specified in each control group until the wounds healed.

Ethical Clearance

In this research mice were used as experimental animals. This research had been declared as reliable by the Health Research Ethics Committee of Faculty of Medicine and Health Science UIN Maulana Malik Ibrahim Malang number 021/EC/KEPK-FKIK/2021

RESULTS AND DISCUSSION

Extraction

With a yield of 22.95% from 500 g of extraction powder yielded a total of 114.76 g of 70% ethanol extract. Alkaloids, anthocyanins, and tannins make up the majority of the pomegranate extract's chemical makeup, followed by flavonoids and polyphenols at 30% each. One of the biggest subgroups of natural phenols are flavonoids. As a result, it has applications and advantages, such as being an anti-inflammatory, antioxidant, or antibacterial (Celiksoy *et al*., 2020; Kurniawan *et al*., 2018; Asadi *et al*., 2018).

Effectiveness Against Cuts Test

Three reactions were seen in the effectiveness test for cuts, including a shortening of the incision's length, a higher percentage of the wound healing, and a shorter incision's healing time. Table 1 displays the average shrinkage outcomes for the incision's length.

Table 1 displays the study's findings. It demonstrates that from the first to the last day of each therapy, the length of the mice's incisions decreased. Group K (3), which received a dose of

Table 1. Average Length of Cuts in Each Group

Days to	Average Length of Cuts for each group (cm) (mean ± SD)				
	K (+)	K (-)	K (1) 7%	K (2) 14%	K (3) 28%
1	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00
2	9.80 ± 0.00	9.90 ± 0.18	9.80 ± 0.15	9.80 ± 0.13	9.30 ± 0.15
5	8.70 ± 0.23	9.10 ± 0.23	8.90 ± 0.19	8.60 ± 0.22	8.10 ± 0.64
8	6.10 ± 0.59	7.70 ± 0.50	6.70 ± 0.61	5.90 ± 0.67	6.20 ± 0.62
11	4.80 ± 0.91	7.20 ± 0.65	5.50 ± 0.46	4.50 ± 0.88	4.00 ± 0.90
14	3.40 ± 0.85	5.50 ± 0.49	4.40 ± 0.60	3.60 ± 0.91	1.20 ± 1.18

Table 2. Average Percentage of Healing of Cuts

Days to	Average Percentage of Healing of Cuts for each group (%) (mean ± SD)				
	K (+)	K (-)	K (1) 7%	K (2) 14%	K (3) 28%
1	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	1.60 ± 1.52	1.20 ± 1.79	1.60 ± 1.52	1.80 ± 1.30	6.80 ± 1.48
5	13.40 ± 2.30	9.40 ± 2.30	11.20 ± 1.92	14.20 ± 2.17	19.00 ± 6.36
8	39.20 ± 5.89	23.00 ± 4.95	32.80 ± 6.10	45.00 ± 9.72	36.60 ± 6.23
11	51.80 ± 9.09	27.80 ± 6.53	32.80 ± 6.10	55.00 ± 8.31	59.80 ± 9.01
14	65.60 ± 8.50	45.40 ± 4.93	56.00 ± 5.96	64.40 ± 8.91	87.80 ± 11.80

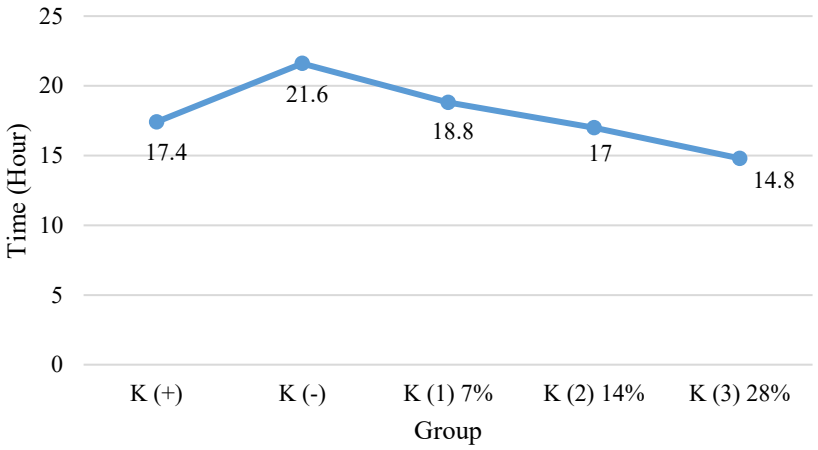

Figure 1. Average results of wound healing time

28% on the second and fifth days, experienced the greatest shrinkage compared to the other groups. In comparison to the other groups, group K (2)'s shrinkage lasted the longest on the eighth day with a dose of 14%. Group K (3) with a dose of 28% showed the greatest shrinkage on days 11 and 14.

The length of the incision in mice varied significantly between groups, as evidenced by statistical analysis, which indicated a significance level of 0.000. The LSD test results revealed that treatment K (3), which involved making a 10 mm diameter burn wound on the backs of the mice and applying 28% pomegranate extract topically, had the lowest mean length of the incision over the course of the observation period. Meanwhile, the K (-) group had the longest average length of incisions, indicating that mice that did not receive any therapy had a more serious disease than other mice.

The average proportion of wound healing outcomes, which are displayed in Table 2, is the following observation regarding incisions.

According to Table 2's findings, each group's proportion of cuts that healed from the first to the last day increased. On the second and fifth days, group K (3) showed the greatest % growth, while group K (-) showed the greatest percentage decrease. On the eighth day, group K (2) had the highest healing % and group K (-) had the lowest. However, on days 11 and 14, group K (3) had the highest percentage of wound healing while group K (-) had the lowest proportion. According to the statistical analysis, there was a significant difference between the groups in the percentage of wound healing. The LSD test was conducted afterward, and the findings demonstrated that the treatments under comparison differed significantly. The Control (-) treatment had the smallest average percentage of wound healing throughout the observation period, according to these results, indicating that mice that received no therapy had a lower percentage of wound healing than mice who received other treatments. In group K (3), the average percentage of wound healing was found to be the greatest, demonstrating that this

treatment was the most successful in terms of the mice's percentage of wound healing.

The next parameter is the average test results for the length of time the incisions heal between groups which can be observed in Figure 1.

Based on Figure 1, there are differences in healing time between groups. This finding was also supported by the results of the statistical analysis, which obtained a significance value of 0.000, which meant that there was a significant difference in the average length of wound healing between treatment groups. The fastest wound healing time was in group K (C) and the longest time was in group K (-). These findings show that in the treatment group the largest extract provides the greatest effectiveness so that the healing process takes more time. Flavonoids are the largest group of natural phenols that can enhance the wound healing process because they have anti-bacterial and anti-inflammatory activity. The content of saponins in pomegranate can stimulate the growth of collagen, and tannins which can increase the formation of dermis tissue (Isrofah *et al*., 2015).

Effectiveness Against Burns Test

Similar to the effectiveness test for cuts, three responses—a decrease in burn diameter, a percentage of burns healing, and how long it takes for burns to heal—were seen in the effectiveness test for burns. Table 3 displays the average shrinking results in the burn's diameter.

Table 3 contains the study's findings. It demonstrates that the diameter of the burn decreased in each test group. The findings showed that throughout the 14 days of observation, group K (-) had the biggest diameter while group K (3) had the least diameter among the other groups. The results of statistical tests, specifically the LSD test, which revealed that treatment K (3)—where second-degree burns were made on the backs of mice with a diameter of 10 mm and smeared with 28% pomegranate extract—obtained the smallest average diameter of burns during the observation period—also supported this finding. topically. The average burn diameter in treatment K (3) was 6.68, and this treatment was the most successful in lowering burn diameter in mice, according to a different notation from all other treatments. The mice that did not receive any therapy had a more serious condition than other animals, as evidenced by the fact that K (-) (8.42) had the burns with the highest average diameter.

Table 3. Average Burn Diameter for each group

Days to	Average Burn Diameter of each group (cm) (mean ± SD)				
	K (+)	K (-)	K (1) 7%	K (2) 14%	K (3) 28%
1	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00
2	9.67 ± 0.06	9.71 ± 0.07	9.67 ± 0.06	9.58 ± 0.06	9.52 ± 0.10
5	8.75 ± 0.10	8.99 ± 0.06	8.75 ± 0.10	8.20 ± 0.22	8.08 ± 0.18
8	7.94 ± 0.14	8.44 ± 0.20	7.94 ± 0.14	7.45 ± 0.11	7.07 ± 0.10
11	5.31 ± 0.23	5.43 ± 0.22	5.31 ± 0.23	4.92 ± 0.12	4.05 ± 0.17
14	3.26 ± 0.27	3.89 ± 0.20	3.26 ± 0.27	2.60 ± 0.19	1.33 ± 0.10

Table 4. Average Percentage Results for Burns Healing

Days to	Average Percentage of Burns Healing for each group (%) (mean ± SD)				
	K (+)	K (-)	K (1) 7%	K (2) 14%	K (3) 28%
1	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	5.76 ± 1.37	4.78 ± 0.38	6.56 ± 1.24	8.20 ± 1.25	9.32 ± 1.89
5	19.24 ± 1.14	10.50 ± 2.29	23.42 ± 1.83	32.68 ± 3.48	34.64 ± 2.86
8	28.76 ± 3.41	24.06 ± 1.04	36.98 ± 2.30	44.52 ± 1.62	49.98 ± 1.40
11	70.42 ± 2.38	42.08 ± 7.80	71.78 ± 2.36	75.82 ± 1.24	83.56 ± 1.38
14	84.86 ± 1.56	72.70 ± 1.60	89.34 ± 1.79	92.74 ± 0.87	98.20 ± 0.29

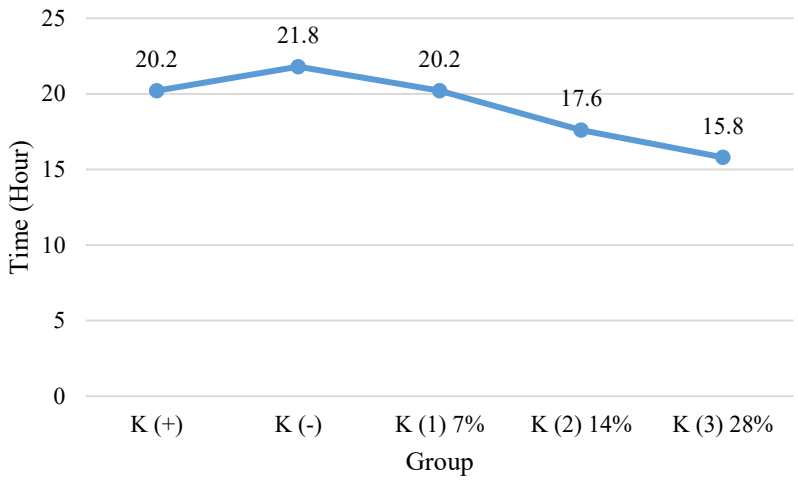

Figure 2. Average results of burn healing time

The average rate of burn wound healing, which is displayed in Table 4, is the next observation regarding burns.

The healing percentage's findings indicate that healing is progressing daily. The results showed that the p value was 0.000, where the p value <5% indicated that there was a significant difference in the percentage of mice burn healing between each group. In each group, there was a difference in increase, which was also verified by statistical tests. Group K (3) had the highest percentage of burn healing, according to the size of the rise. The LSD test results, which showed that group K (3) had the highest average percentage of burn healing (45.9%), which suggested that this treatment was the most effective in terms of the percentage of healing of burns in the other groups, confirm this. While treatment K (-), where the average result was 26.4%, had the lowest average percentage of burn healing throughout the observation period, it showed that mice that received no therapy had worse healing conditions than mice that received other treatments.

The second finding was that burns take a longer time to heal (see Figure 2). The K (3) treatment group had the quickest burn healing times, while the K (-) group had the slowest healing times, according to the results.

According to the statistical analysis, group K (3) had the quickest average healing time for burns, lasting 15.8 days, which showed that mice treated topically with 28% pomegranate extract after receiving second-degree burns recovered more quickly than mice receiving other treatments. The K (-) group had the longest average healing time for burns (21.8 days), demonstrating that mice with second-degree burns who did not get any treatment recovered far more slowly than those that got other therapies.

Both of the wound types used in this study contain risk factors for complications, which can in many respects make the healing process worse. In this study, infection was the most likely side effect. Therefore, topical medicines need to have an antibacterial component. Both of these components are affordable, effective against both gram-negative and gram-positive bacteria, and free of severe side effects (Lukiswanto *et al*., 2019. Due to its ability to effectively manage wound complications, pomegranate extract is used in topical therapeutic formulations. This extract has many advantages, including the ability to moisturize the skin for a longer period of time, the ability to avoid contact between the skin's surface and external stimuli, and the ease with which it may be applied and absorbed by the skin (Isrofah *et al*., 2015). The topical medicines utilized are gels because they offer various benefits, including being readily applied to the skin, leaving no visible traces, and producing a cooling sensation (Afiani, 2015). The gelling agent Sodium Carboxy Methyl Cellulose (Na-CMC) is used in wound healing gel compositions. As a cellulose derivative, Na-CMC possesses neutral characteristics, is resistant to microbial development, and when dried, forms a strong film (membrane) and transparent gel base on the skin. It also has a constant viscosity (Hariningsih, 2019).

Pomegranates, in general, have a variety of active ingredients that each function as potent

antioxidants, antibacterials, and anti-inflammatory agents. Polyphenols including saponins, flavonoids, and hydrolyzed tannins are among these components (Celiksoy *et al*., 2020; Lukiswanto *et al*., 2019; Asadi *et al*., 2018). For the skin to recover naturally, tannins in particular can function as a natural astringent and wound protection (Fadhilah *et al*., 2022; Kurniawan *et al*., 2018). Pomegranate has been shown in earlier studies to play a similar role to ampicillin. Pomegranate active ingredients can produce toxicity in the bacterial body through modifications and interactions with enzymes and substrates, while the exact antibacterial mechanism is still unknown (Kurniawan *et al*., 2018). Cyclooxygenase-2 (COX-2) is expressed during the inflammatory process, which encourages the creation of prostaglandins (PG). In this study, it was found that the pomegranate's active ingredient can reduce COX-2 expression through its anti-inflammatory properties (Gunter *et al*., 2017). Because prolonged inflammation can produce too many reactive oxygen species (ROS) and oxidative stress is a fundamental factor in the destruction to the host's connective tissue, strong antioxidant activity can play a significant role in wound healing. Pomegranate polyphenols, which are potent antioxidants, help to keep levels of glutathione, malondialdehyde, glutathione peroxidase, and catalase stable, so helping to reduce oxidative stress and ROS damage (Celiksoy *et al*., 2020; Lukiswanto *et al*., 2019).

CONCLUSIONS

The ability to significantly speed up the healing of cuts and burns in mice at an optimal dose of 28% at nearly every day group is demonstrated by a reduction in the length of the incision, a reduction in the diameter of the burn, and an increase in the percentage of the healing of cuts and burns following administration of a 70% ethanol extract of pomegranate fruit. This finding demonstrates the ability of pomegranate extract to effectively and safely treat wounds.

CONFLICT OF INTEREST

There is no conflict of interest.

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REFERENCES

Afiani N., Santoso S., Handayani T., Yahya F.N. 2019. Efektifitas debridemen mekanik pada luka bakar derajat III terhadap kecepatan penyembuhan luka. *JKEP,* 4(2), 93-103.

Ali, M. B., and Ali, M. B. 2022. Psychological and physiological complications of post-burn patients in Pakistan: A narrative review. *Sultan Qaboos University Medical Journal*, 22(1), 8–13.

Almuhayawi, M. S., Ramadan, W. S., Harakeh, S., Al Jaouni, S. K., Bharali, D. J., Mousa, S. A., and Almuhayawi, S. M. 2020. The potential role of pomegranate and its nano-formulations on cerebral neurons in aluminum chloride induced Alzheimer rat model. *Saudi Journal of Biological Sciences*, 27(7), 1710–1716.

Anggowarsito, J. S. 2014. Luka bakar sudut pandang dermatologi. *Jurnal Widya Medika Surabaya*, 2(2), 115-120.

Asadi, M. S., Mirghazanfari, S. M., Dadpay, M. and Nassireslami, E., 2018. Evaluation of wound healing activities of pomegranate (*Punica granatum*-Lythraceae) peel and pulp. *Journal of Research in Medical and Dental Science*, 6(3), 230–236.

Celiksoy, V., Moses, R. L., Sloan, A. J., Moseley, R., and Heard, C. M. 2020. Article evaluation of the in vitro oral wound healing effects of pomegranate (*Punica granatum*) rind extract and punicalagin, in combination with zn (ii). *Biomolecules*, 10(9), 1–15.

Eghbali, S., Askari, S. F., Avan, R., and Sahebkar, A. 2021. Therapeutic effects of *Punica granatum* (Pomegranate): An updated review of clinical trials. *Journal of Nutrition and Metabolism,* 5297162.

Faddladdeen, K., and Ojaimi, A. 2019. Protective effect of pomegranate (*Punica granatum)* extract against diabetic changes in adult male rat liver: Histological study. *Journal of Microscopy and Ultrastructure, 7(4), 165.*

Fadhilah, H., Indah, F. P. S., and Febriza, S. 2022. Studi literatur efektivitas tanaman terhadap penyembuhan luka sayat. *Edu Masda Journal*, 6(1), 1.

Farina, J.A., Rosique, M.J., Rosique, R.G. 2013. Curbing inflammation in burn patients. *International Journal of Inflammation*, Vol 2013, 715645.

Gunter, B. R., Butler, K. A., Wallace, R. L., Smith, S. M., and Harirforoosh, S. 2017. Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: A meta-

analysis. *Journal of clinical pharmacy and therapeutics*, 42(1), 27–38.

Hariningsih, Y. 2019. Pengaruh variasi konsentrasi Na-CMC terhadap stabilitas fisik gel Ekstrak pelepah Pisang Ambon (*Musa paradisiaca* L.). *Parapemikir : Jurnal Ilmiah Farmasi,* 8(2), 46–51.

Harris, A., Amran, C. M. F., Salim, M. N., Balqis, U., Armansyah, T., Karmil, T. F., and Riady, G. 2020. 39. Efficacy of Jatropha cream (Jatropha curcas L.) on maturation phase of cutaneus healing process in Mice (*Mus musculus*). *Jurnal Medika Veterinaria*, 13(2), 274–280.

Hertian, R., Muhaimin, and Sani K, F. 2021. Uji efektivitas ekstrak Daun Ekor Naga (Rhaphidohora pinnata (L.f) Schott) terhadap penyembuhan luka sayat pada mencit putih jantan. *Indonesian Journal of Pharma Science,* 1(1), 5–24.

Isrofah, Sagiran, Afandi, M. 2015. Efektifitas salep ekstrak Daun Binahong (Anredera cordifolia (Ten) Steenis) terhadap proses penyembuhan luka bakar derajat 2 termal pada tikus putih *(Rattus novergicus*). *Indonesian Journal of Nursing Practices*, 2(1), 27-39.

Kurniawan, J., Edrizal, E., and Desnita, E. 2018. Efektifitas estrak Buah Delima (*Punica granatum*) secara topical dalam proces pemyembuhan luka mukosa pada tikus putih (Galur Wistar). B-Dent, Jurnal Kedokteran Gigi Universitas Baiturrahmah, 1(2), 126–133.

Lukiswanto, B. S., Miranti, A., Sudjarwo, S. A., Primarizky, H., and Yuniarti, W. M. 2019. Evaluation of wound healing potential of pomegranate (*Punica granatum*) whole fruit extract on skin burn wound in rats (Rattus norvegicus). *Journal of advanced veterinary and animal research*, (6)2, 202-207.

Michicotl-Meneses, M. M., Thompson-Bonilla, M. D. R., Reyes-Lopez, C. A., Garcia-Perez. B. E., Lopez-Tonorio, I., I., and Ordaz-Pichardo, C., and Jaramillo-Flores, M. E. 2021. Inflammation markers in adipose tissue and cardiovascular risk reduction by Pomegranate juice in obesity induced by a hypercaloric diet in Wistar rats. *Nutrients,* 13(8), 2577.

Moga, M. A., Dimienescu, O. G., Balan, A., Dima, L., Toma, S. I., Bîgiu, N. F., and Blidaru, A. 2021. Pharmacological and therapeutic properties of *Punica granatum* phytochemicals: Possible roles in breast cancer. *Molecules*, 26(4), 1054.

Purwanto, D. S., and Astrawinata, D. A. W. 2018. Mekanisme kompleks sepsis dan syok Septik. *Jurnal Biomedik* (JBM), 10(3), 143.

Ramadhian, M. R., and Widiastini, A. A. 2018. Tinjauan pustaka kegunaan ekstrak daun Pepaya (Carica papaya) pada luka. *Jurnal Kesehatan dan Agromedicine*, 5(1), 513–517.

Sani K, F., Rahman, H., and Rahman, A. O. 2022. Efektivitas khasiat penyembuhan luka sayat gel ekstrak etanol Daun Ekor Naga (*Rhaphidophora pinnata* (L.f) Schott) berdasarkan analisis hidroksiprolin. *Jurnal Farmasi Sains dan Terapan*, 9(2), 60–66.

Wang, D., özen, C., Abu-Reidah, I. M., Chigurupati, S., Patra, J. K., Horbanczuk, J. O., Józwik, A., Tzvetkov, N. T., Uhrin, P., and Atanasov, A. G. 2018. Vasculoprotective effects of pomegranate (*Punica granatum* L.). *Frontiers in Pharmacology*, 9(May), 1–15.

Zhang, L., Yang, R., Hu, Y., Yang, Y., Zhang, X., He, B., Shen, Z., Yang, J. Y., and Chen, P. 2022. Promoting effect of pomegranate peel extract on second-degree burn wound-healing through VEGF-A and TGF-β1 regulation. *Burns*, 48(3), 639–648.