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The role of Manalagi apple (*Malus sylvestris* Mill.) extract gel in fibronectin expression during traumatic ulcer healing

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ABSTRACT

Traumatic ulcer is open wound caused by injury to the oral mucosa. Fibronectin, a multifunctional glycoprotein, has been reported to play a crucial role in early wound healing by promoting fibroblast migration. Several studies have shown that Manalagi apple (*Malus sylvestris* Mill.) contains bioactive compounds with anti-inflammatory, antioxidant, antibacterial, and wound healing properties. Therefore, this study aims to evaluate the effect of Manalagi apple extract gel on fibronectin expression in traumatic ulcer healing. This was a laboratory experimental study with a post-test only control group design. A total of 10 rats (*Rattus norvegicus*) were randomly divided into a placebo gel control group and a treatment group receiving 10% Manalagi apple extract gel. Fibronectin expression was then evaluated using immunohistochemical (IHC) staining, and analyzed with the Mann–Whitney test. The results showed a significant difference in fibronectin expression between the treatment and control groups (p = 0.007). The application of 10% Manalagi apple extract gel significantly increased fibronectin expression during traumatic ulcer healing.

Keywords: Fibronectin; Traumatic Ulcer; Wound Healing; Apple; Plant Extracts

ABSTRAK

Ulkus traumatik merupakan luka terbuka yang disebabkan oleh cedera pada mukosa oral. Fibronectin, sebagai glikoprotein multifungsi, berperan penting pada tahap awal penyembuhan luka dengan meningkatkan migrasi fibroblas. Apel Manalagi (*Malus sylvestris* Mill.) mengandung senyawa bioaktif dengan sifat antiinflamasi, antioksidan, dan antibakteri yang dapat mendukung proses penyembuhan luka. Penelitian ini bertujuan untuk mengevaluasi pengaruh gel ekstrak apel Manalagi terhadap ekspresi fibronectin pada penyembuhan ulkus traumatik. Penelitian eksperimental laboratoris ini menggunakan desain *post-test only control group*. Sebanyak 10 ekor tikus (*Rattus norvegicus*) dibagi secara acak menjadi kelompok kontrol gel plasebo dan kelompok perlakuan yang diberikan gel ekstrak apel Manalagi 10%. Ekspresi fibronectin dinilai menggunakan pewarnaan imunohistokimia dan dianalisis dengan uji Mann–Whitney. Hasil penelitian menunjukkan adanya perbedaan signifikan ekspresi fibronectin antara kelompok perlakuan dan kontrol (p = 0,007). Pemberian gel ekstrak apel Manalagi 10% secara signifikan meningkatkan ekspresi fibronectin selama proses penyembuhan ulkus traumatik.

Kata kunci: Fibronektin; Ulkus Traumatik; Penyembuhan Luka; Ekstrak Apel

1. Introduction

Traumatic ulcer is open wound that is generally caused by physical trauma, such as accidental biting of cheek or tongue, as well as irritation from acrylic denture bases and fractured teeth. This wound is also caused by improper use of dental instruments, overly vigorous tooth brushing, chemical trauma, or thermal injury. Patients with traumatic ulcer typically experience pain and tenderness when the affected area is touched, as well as discomfort during eating, speaking, and swallowing [1]. The prevalence of traumatic ulcer is relatively high, with epidemiological studies reporting rates ranging from 3% to 24% of the population. The wound is considered among the most commonly encountered oral mucosal conditions in Indonesia, but the reported prevalence varies depending on study design and population characteristics [2–5]. Wound healing in traumatic ulcer occurs through a complex and regulated process consisting of hemostasis, inflammation, proliferation, and remodeling phases [6]. During the early stages, extracellular matrix (ECM) components play a critical role in supporting cell migration and tissue repair [7,8]. Among these, fibronectin is a key glycoprotein that facilitates fibroblast adhesion, migration, and matrix organization, making it an important biomarker for evaluating early wound healing activity [9–11]. Despite its central role, studies specifically evaluating the modulation of fibronectin expression in oral traumatic ulcer healing remain limited, particularly in the context of natural or herbal therapeutic agents [2,12–16].

One of the treatments for traumatic ulcer is the application of topical corticosteroids, such as 0.1% triamcinolone acetonide. However, the treatment may cause adverse effects, including burning sensation, stinging, itching, desquamation, and oral mucosal atrophy[17]. These adverse effects have prompted increasing interest in alternative therapies derived from natural products. Herbal-based treatments are often considered safer and more accessible, but their mechanisms of action, standardization, and clinical efficacy remain insufficiently explored, indicating the need for more evidence-based investigations [18–23]. Apple (*Malus sylvestris* Mill.) has been reported to contain various bioactive compounds, including flavonoids, polyphenols, terpenoids, tannins, and saponins, which exhibit antioxidant, anti-inflammatory, and potential wound-healing properties. Among local varieties, Manalagi apple is widely available in Indonesia and have demonstrated a rich phytochemical profile [24–26]. Compounds, such as saponins, are suggested to promote wound healing by stimulating fibroblast activity, enhancing fibronectin synthesis, and modulating the expression of transforming growth factor-β (TGF-β) receptors. Meanwhile, flavonoids such as quercetin contribute to oxidative stress reduction and tissue repair by enhancing fibroblast proliferation, collagen deposition, and angiogenesis [27–31]. Despite existing literature, current evidence is largely limited to general wound-healing effects, and there is still a lack of specific data explaining how apple-derived compounds influence fibronectin expression in oral mucosal wound.

The administration of apple extract in gel form aims to facilitate drug delivery to mucosal tissues, including the oral mucosa. Gel formulations offer several advantages, such as prolonged contact time with the tissue surface, strong adhesion, ease of removal, and efficient release of active compounds [32]. Previous studies have investigated apple extract gel at various concentrations. Baiti et al. compared apple extract gel concentrations of 10%, 15%, and 20%, reporting that the 10% level exhibited the highest antioxidant activity [27]. However, selecting a concentration solely based on antioxidant capacity may not fully reflect its effectiveness in modulating specific wound healing mechanisms. Antioxidant activity plays an important role in reducing oxidative stress during the early phase of wound healing, which may indirectly support fibroblast function and extracellular matrix formation, including fibronectin synthesis. The 10% concentration was selected in this study not only based on antioxidant potential but also due to its presumed ability to create a favorable microenvironment for fibroblast activity and matrix deposition. The direct effect on fibronectin expression in traumatic ulcer healing has not yet been clearly established and requires further investigation. Therefore, this study aims to investigate the effect of 10% Manalagi apple extract gel on fibronectin expression during healing process of traumatic ulcer. The current study specifically addressed the existing gap regarding the molecular mechanism of apple extract in modulating early wound healing, with fibronectin selected as a primary outcome due to its critical role in extracellular matrix formation and tissue repair.

2. Materials and Methods

This study used a laboratory experimental design with a post-test only control group design. The sample size was calculated using the Lemeshow formula, with an additional 10% included to account for potential sample dropout, leading to a minimum of 5 animals per group. In addition, the sample size was adjusted considering ethical principles for animal studies to minimize the number of animals used while maintaining statistical validity. Samples were selected using simple random sampling, involving 10 male Wistar strain white rats (*Rattus norvegicus*), which were divided into 2 groups. The preparation of apple extract and apple

extract gel was conducted at the Pharmacology Laboratory, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya. The experimental procedures involving Wistar rats were carried out at the Biochemistry Laboratory, Faculty of Medicine, Universitas Airlangga, Surabaya. Meanwhile, the analysis of fibronectin expression during healing process of traumatic ulcer was performed at the Research Center, Universitas Airlangga, Surabaya. The study procedures were conducted from May to June 2024.

2.1 Instruments and Materials

The instruments used in this study included experimental animal cages, animal feeding and drinking containers, sealed jars and bottles, a microtome (Leica RM 2135), rotary evaporator (IKA, Malaysia), vacuum infiltration processor, Eppendorf tubes, Büchner funnel, Erlenmeyer flasks (Iwaki, Indonesia), filter paper (Whatman No. 1), staining jars (Sakura, Japan), burnisher, and analytical balance (KERN ABS, Germany). Others included an Eclipse Ci microscope, scalpel blades, micro brushes, anatomical forceps, paraffin molds, graduated cylinders (Pyrex, Japan), hot plate, Bunsen burner, beaker glasses (Pyrex, Japan), electric stirrer, water bath (Memmert, Germany), microscope slides (Citoplus), electric microscope (Olympus CX21), and syringes (One Med, Germany).

The materials used consisted of male Wistar strain rats (Rattus norvegicus), 10% apple extract gel, placebo gel, 70% ethanol, 10% buffered formalin, alcohol, xylene/toluene solution, aniline blue solution, paraffin (Histoclast), CMC-Na (carboxymethylcellulose sodium), clindamycin, ketamine and xylazine (PT Guardian Pharmatama), and A16678 Fibronectin Rabbit polyclonal antibody (100 µL).

2.2 Procedures

The study preparation began with obtaining ethical clearance, followed by the preparation of experimental animals and materials. The experimental animals consisted of 10 male Wistar strain rats (*Rattus norvegicus*), aged 3 to 4 months and weighing 150 to 200g. Material preparation required extracting 6 kg of Manalagi apple using the maceration method with 96% ethanol as the solvent. The resulting concentrated apple extract was subsequently formulated into a gel. Gel formulation was prepared using CMC-Na as the primary base, to which 100 mL of distilled water was added and mixed using an electric stirrer for 6 hours. The concentrated apple extract was incorporated into CMC-Na gel base to obtain a 10% apple extract gel formulation.

Traumatic ulcer was induced using a ball burnisher heated over a Bunsen burner until reaching a red-hot condition (approximately 45 seconds of heating), following previously established protocols. Subsequently, the heated burnisher (approximately 2 mm in diameter) was gently applied to the lower labial mucosa of the experimental animals for 1 to 3 seconds without excessive pressure, with a controlled depth of no more than 1 mm. All procedures were performed by the same operator to ensure consistency. The induced lesions were expected to produce circular ulcers with a diameter of approximately 2–3 mm. Ulcer formation was observed in 24 hours, characterized by round lesions with erythematous margins and a whitish-yellow ulcer base [18,33,34]. Before ulcer induction, each animal was anesthetized with ketamine and xylazine at a dose of 0.2 mL. Rats were then divided into 2 groups, namely a treatment group receiving 10% apple extract gel and a control group receiving placebo gel. The treatments were administered topically for 6 days, twice daily, in the morning at 09:00 a.m. and in the afternoon at 05:00 p.m. After the treatment period, the animals were euthanized.

The lower labial mucosal tissue was excised using surgical scissors, and the ulcerated area was removed with a scalpel. Tissue samples were sectioned to a thickness of 2 to 3 mm with a size of approximately 0.5 to 1 cm to obtain optimal specimens. Paraffin-embedded tissue preparation included tissue fixation, selection, dehydration, block formation, sectioning, staining, and mounting. Immunohistochemical (IHC) staining was performed to evaluate fibronectin expression. Paraffin-embedded tissue sections were deparaffinized in xylene and rehydrated through a graded ethanol series. Antigen retrieval was carried out with a heat-induced method, while endogenous peroxidase activity was blocked using hydrogen peroxide, followed by incubation with a primary antibody against fibronectin (A16678 Fibronectin Rabbit polyclonal antibody) overnight at 4°C. The sections were then incubated with a secondary antibody and visualized using a chromogen (DAB). Counterstaining was performed using hematoxylin. The stained sections were observed under a light microscope, and fibronectin expression was quantified using ImageJ software.

2.3 Ethical Approval

The study protocol was approved by the Research Ethics Committee of the Institut Ilmu Kesehatan Bhakti Wiyata Kediri, with ethical clearance number 316/FKG/EP/IV/2024. All experimental procedures were

conducted in accordance with institutional guidelines for animal care and use. Before ulcer induction, animals were anesthetized using an appropriate anesthetic protocol to minimize pain and distress. In the study, the animals were monitored daily for general health conditions, signs of pain or discomfort, and wound progression. Humane endpoints were established, and any animals showing signs of severe distress, infection, or significant weight loss were excluded from the study and provided appropriate care.

2.4 Data Analysis

IHC scoring data were analyzed using SPSS software. Before analysis, data distribution was assessed using the Shapiro–Wilk test. As the data were not normally distributed ($p < 0.05$), a non-parametric Mann–Whitney test was used to compare differences between groups.

3. Results

IHC examination showed fibronectin expression, which was quantified using ImageJ analysis software. The treatment group showed increased fibronectin expression compared to the control group (Figure 1). Representative images were selected based on the most consistent staining pattern observed across samples in each group.

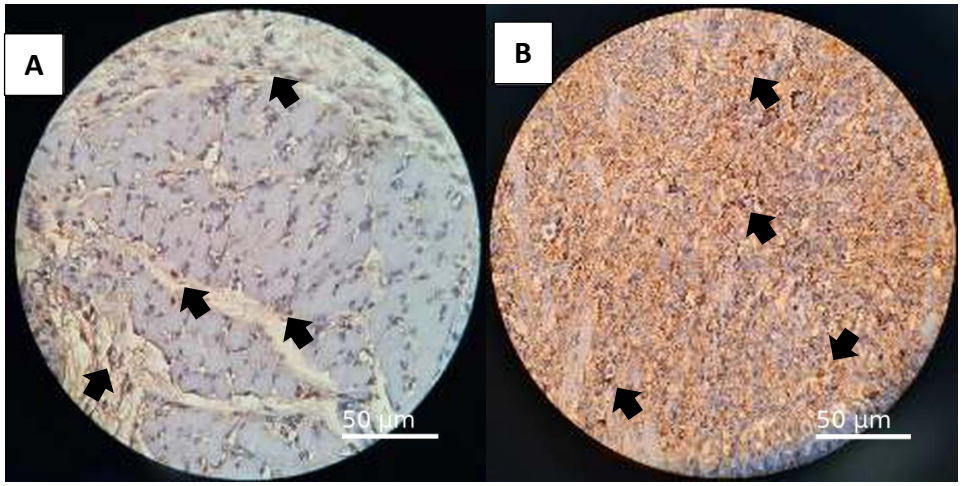

Figure 1. IHC staining of fibronectin expression in traumatic ulcer tissue. Positive fibronectin expression was indicated by brown staining (arrow), primarily localized in the extracellular matrix and surrounding fibroblast cells within the connective tissue. Images were captured at x400 magnification. (A) Placebo gel control group showing a score of 1; (B) Treatment group treated with 10% Manalagi apple extract gel showing a score of 3.

Based on statistical analysis using SPSS and the non-parametric Mann–Whitney test, fibronectin expression data were presented as median (interquartile range, IQR) (Table 1).

Table 1. Comparison of fibronectin expression between placebo and 10% Manalagi apple extract gel groups (median [IQR])

Sample	Placebo gel	10% Manalagi apple extract gel
1	23.297	48.519
2	19.518	52.311
3	24.662	58.514
4	26.637	56.124
5	22.462	54.201
Median (IQR)	23.297 (22.462-24.662)	54.201 (52.311-56.124)

The results showed that the treatment group exhibited higher fibronectin expression (54.201 [52.311–56.124]) compared to the placebo group (23.297 [22.462–24.662]). Statistical analysis using the Mann–Whitney test demonstrated a significant difference between the two groups ($p = 0.007$; $p < 0.05$).

Histopathological evaluation using IHC staining further supported these results. Fibronectin expression was assessed semi-quantitatively using the scoring criteria proposed by Kawasaki et al. [35] The placebo group predominantly showed weak expression (score 1; 1–25%), while the treatment group demonstrated strong expression (score 3; 51–75%).

These semi-quantitative scoring results were consistent with the quantitative ImageJ analysis, showing that the application of 10% Manalagi apple extract gel was associated with increased fibronectin expression during traumatic ulcer healing.

4. Discussion

Traumatic ulcer caused by several forms of trauma underwent 4 phases of wound healing, namely hemostasis, inflammation, proliferation, and remodeling [6]. Hemostasis phase is the initial response to injury, during which blood clotting occurs to prevent bleeding. This was followed by the inflammatory phase, which began immediately after injury and lasted until day 5. During this phase, several inflammatory cells were activated, including macrophages, which performed phagocytosis to eliminate bacteria through the production of reactive oxygen species (ROS). In addition, macrophages secrete growth factors that stimulate angiogenesis and fibroblast formation. Connective tissue formation occurred through fibrin and fibronectin derived from the blood [36].

Wound entered the acute inflammatory phase, which removed necrotic tissue and combated pathogenic bacterial infection. Subsequently, wound progressed into the proliferative phase, occurring between days 3 and 14, including macrophages that were gradually replaced by extracellular matrix components and fibroblasts. During this phase, keratinocyte proliferation accelerated epithelialization, while fibronectin present at wound site initiated extracellular matrix formation, which was rapidly populated by proliferating fibroblasts. The final phase was the remodeling phase, which occurred from day 21 up to 1 year and included fibroblasts differentiating into myofibroblasts that contract to close wound area [37].

Manalagi apple contained various bioactive compounds such as flavonoids, terpenoids, polyphenols, tannins, and saponins [25], which contributed to the stimulation of fibronectin formation and acceleration of wound healing. Flavonoids and terpenoids promoted wound healing by inhibiting key stages in the cyclooxygenase pathway biosynthesis and exerting anti-inflammatory effects that reduced prostaglandin production during inflammation [38]. Polyphenols functioned as antioxidants and possessed antibacterial activity in wound healing [39]. Tannins enhanced wound contraction, promoted capillary blood vessel formation, and activated fibroblasts [40]. Saponins accelerated wound healing by stimulating collagen formation, enhancing fibronectin synthesis by fibroblasts, and modulating the expression of TGF-β receptors. In wound healing process, fibronectin served as a regulator of cellular processes and was an essential protein for maintaining tissue adhesion and extracellular matrix composition, as well as being included in cell adhesion, migration, and differentiation [12].

Based on the results of this study, the treatment group receiving 10% Manalagi apple extract gel demonstrated higher fibronectin expression due to the presence of bioactive compounds such as terpenoids, tannins, saponins, quercetin, pectin, chlorogenic acid, epicatechin, and polyphenols, especially flavonoids, flavan-3-ols, and flavonols [25,41–44]. These compounds possessed anti-inflammatory, antioxidant, and antibacterial properties that contributed to enhanced stimulation of fibronectin formation and accelerated wound healing [13,45–47].

Topical application of 10% Manalagi apple extract gel was effective in increasing fibronectin expression in injured tissue. Gel formulation offered several advantages, including the presence of hydrophilic and hydrophobic gel bases that provided a cooling sensation upon application, strong tissue adhesion, ease of removal with water, and effective drug release [32]. Moreover, the 10% Manalagi apple extract gel was non-toxic and safe for health use.

Based on the measurement of fibronectin expression presented in Table 1, the results showed that the application of 10% Manalagi apple extract gel led to the highest mean fibronectin expression (53,934) compared to the placebo group, suggesting an enhanced biological response associated with tissue repair. Fibronectin played a significant role in wound healing process by facilitating cell adhesion, migration, and extracellular matrix formation. Therefore, its increased expression showed a more active and effective healing environment [9,10,48,49]. The Mann–Whitney test demonstrated a statistically significant difference between the treatment and control groups, with a p-value of 0.007 ($p < 0.05$). This statistically significant result showed that the observed increase in fibronectin expression was not due to random variation alone. Collectively, these

results suggested that the 10% Manalagi apple extract gel had a measurable and meaningful effect in promoting wound healing, as evidenced by the elevated fibronectin levels compared to placebo gel.

The increased fibronectin expression observed in this study suggested that the 10% Manalagi apple extract gel enhanced the proliferative phase of wound healing, particularly through modulation of fibroblast activity and extracellular matrix formation. This effect could be explained by the presence of bioactive compounds, particularly flavonoids and saponins [7–9]. Flavonoids, such as quercetin, exhibited antioxidant and anti-inflammatory properties that reduced oxidative stress and created a favorable microenvironment for fibroblast proliferation and migration. This process was essential for fibronectin synthesis and matrix organization [28–31]. Furthermore, saponins were reported to stimulate fibroblast activity and upregulate growth factor signaling pathways, including transforming growth factor-β (TGF-β), which played a major role in fibronectin production, extracellular matrix deposition, and tissue repair [50].

These results were consistent with the previous study by Baiti et al. [27], reporting that 10% apple extract gel exhibited strong antioxidant activity due to flavonoid and polyphenol derivative content, compounds known to prevent and repair cellular damage. The results were consistent with Aprilia [51], which demonstrated anti-inflammatory effects of Manalagi apple extract attributable to flavonoid content. Most previous studies have focused on general wound healing outcomes, such as wound closure and collagen formation. However, this study specifically demonstrated an increase in fibronectin expression, providing more targeted evidence of the molecular processes included in tissue repair. This showed the potential of Manalagi apple extract not only as antioxidant and anti-inflammatory agent but also as a modulator of extracellular matrix dynamics during wound healing. Nevertheless, the precise molecular mechanisms underlying fibronectin upregulation in response to apple extract remained unclear. The interaction between multiple bioactive compounds could produce synergistic effects, but further investigation was required to elucidate the specific signaling pathways required.

The treatment group receiving 10% Manalagi apple extract gel demonstrated a greater potential to stimulate fibronectin expression during healing process of traumatic ulcer. This study had several limitations that must be considered when interpreting the results. First, the relatively small sample size could limit the generalizability of the results. Second, this study evaluated wound healing based on a single biomarker, fibronectin expression, which did not fully represent the complex biological processes required in tissue repair. Third, the observation period was relatively short, thereby limiting the ability to assess long-term healing outcomes and tissue remodeling. Finally, as this study was conducted using an animal model, the results were not directly extrapolated to human clinical conditions. Therefore, further studies with larger sample sizes, longer observation periods, additional biomarkers, and clinical trials in humans were recommended.

5. Conclusion

In conclusion, 10% Manalagi apple extract gel demonstrates potential to enhance fibronectin expression during traumatic ulcer healing in Wistar rats. Broader studies with longer observation and human trials are needed to confirm its therapeutic potential.

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7. Conflict of Interest

The authors declare no conflict of interest regarding the publication of this article.

References

[1]. Khairiati M, W., Bakar A. Ulkus traumatikus disebabkan trauma mekanik dari sayap gigi tiruan lengkap (Laporan kasus). J B-Dent. 2014; 1: 112–7.
[2]. Saadah N, Hendarti HT, Prehananto H. The effect of basil leaves (Ocimum sanctum L.) extract gel to traumatic ulcer area in Rattus norvegicus. JKG 2020; 8: 11–5.

[3]. Soehardy J, Angela T, Angela E. Management of traumatic ulcers in a patient with Angle Class I malocclusion: A case review. JPPIPA 2025; 11: 141–5.
[4]. Dermawan IGNP, Dewi IK, Pramudani NNA. Prevalence of patients with traumatic ulcer at RSGM Saraswati Denpasar in 2023. IJKG 2025; 21: 86–91.
[5]. Siregar FD, Setiadhi R. Traumatic ulcer associated with iatrogenic trauma after basal cell adenoma surgery. Dentika: Dent J 2023; 26: 136–41.
[6]. Singh S, Young A, McNaught CE. The physiology of wound healing. Surgery 2017; 35(9): 473–7.
[7]. Diller RB, Tabor AJ. The role of the extracellular matrix (ECM) in wound healing: A review. Biomimetics. 2022; 7(3).
[8]. Xue M, Jackson CJ. Extracellular matrix reorganization during wound healing and its impact on abnormal scarring. Adv Wound Care 2015; 4(3): 119–36.
[9]. Patten J, Wang K. Fibronectin in development and wound healing. Adv Drug Deliv Rev 2021; 170: 353–68.
[10]. Gimeno-Lluch I, Benito-Jardón M, Guerrero-Barberà G. The role of the fibronectin synergy site for skin wound healing. Cells 2022; 11: 1–17.
[11]. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: A cellular perspective. Physiol Rev 2019; 99(1): 665–706.
[12]. Novita N, Agustina H, Hernowo BS. Analysis of fibronectin and TGF-β1 immunoexpression to determination of wound vitality in Wistar rats (Rattus norvegicus. JMH 2015; 1: 48–60.
[13]. Trinh XT, Long NV, Anh LT. A comprehensive review of natural compounds for wound healing: Targeting bioactivity perspective. Int J Mol Sci 2022; 23.
[14]. Liu E, Gao H, Zhao YJ. The potential application of natural products in cutaneous wound healing: A review of preclinical evidence. Front Pharmacol 2022; 13.
[15]. Yang F, Fang Z, Yang M. Research hotspots in natural products for wound healing: A bibliometric analysis and literature review. Clin Cosmet Investig Dermatol 2025; 18: 1985–97.
[16]. Criollo-Mendoza MS, Contreras-Angulo LA, Leyva-López N. Wound healing properties of natural products: Mechanisms of action. Molecules 2023; 28: 1–18.
[17]. Aripin AN, Andriani D, Ashrin MN. Efek pemberian astaxanthin (Haematococcus pluvialis) terhadap ukuran diameter pada model ulkus traumatikus. JKG 2022; 34: 208–15.
[18]. Dermawan IGNP, Sari NNG, Ardana DY. The role of java cabe. IJKG 2022; 18(2): 74–80.
[19]. Swastirani A, Kembaren CCAS. Pengaruh mucoadhesive plester ekstrak daun ciplukan (Physalis angulata L.) terhadap jumlah limfosit dalam penyembuhan ulkus traumatikus tikus putih (Rattus norvegicus. STOMATOGNATIC 2023; 20: 92–7.
[20]. Xu Z, Dong M, Yin S. Why traditional herbal medicine promotes wound healing: Research from immune response, wound microbiome to controlled delivery. Adv Drug Deliv Rev 2023; 195: 1–21.
[21]. Balkrishna A, Sharma N, Srivastava D. Exploring the safety, efficacy, and bioactivity of herbal medicines: Bridging traditional wisdom and modern science in healthcare. FIM 2024; 3: 35–49.
[22]. Hemanth K, Ramesh Y, Penabaka V. A review on wound healing herbs. GSCBPS 2025; 33: 484–97.
[23]. Setyawati A, Yusuf S, Jafar N. Exploring herbal remedy utilization for wound healing: Patterns, patient preferences, and implications for nursing practice. Int J Nurs Knowl 2024; 35(4): 363–74.
[24]. Pratiwi NN, Prasetyowati S. Efektivitas mengunyah apel jenis Anna dikupas dan tanpa dikupas terhadap penurunan indeks plak. JKG 2020; 7: 59–64.
[25]. Khoiroh N, Lukiati B, Parabaningtyas S. Uji aktivitas antibakteri ekstrak metanol kulit buah apel manalagi (Malus sylvestris Mill.) terhadap bakteri Staphylococcus epidermidis secara in vitro. 2018.
[26]. Novioella AM. Uji aktivitas antioksidan ekstrak etanol dan fraksi etil asetat kulit apel manalagi (Malus sylvestris Mill). Skripsi. Malang. Universitas Islam Negeri Maulana Malik Ibrahim, 2019.
[27]. Kusnadi. P, Baiti AN. Evaluasi sifat fisik dan uji aktivitas antioksidan masker gel peel off ekstrak kulit buah apel manalagi (Phyrus mallus S.) dengan metode spektrofotometri UV-VIS. Pasurungan Lor, Tegal. Politeknik Harapan Bersama, 2021.
[28]. Wu D, Jiang M, Zhang J. Dual role of quercetin in promoting early wound healing via inhibiting inflammatory factors and attenuating scar formation by suppressing myofibroblast differentiation. Front Biosci 2025; 30: 1.
[29]. Carvalho MTB, Araújo-Filho HG, Barreto AS. Wound healing properties of flavonoids: A systematic review highlighting the mechanisms of action. Phytomedicine 2021; 90: 1–15.
[30]. Frenț OD, Stefan L, Morgovan CM. A systematic review: Quercetin—Secondary metabolite of the flavonol class, with multiple health benefits and low bioavailability. Int J Mol Sci 2024; 25: 1–47.
[31]. Huang HC, Chen Y, Hu J. Quercetin and its derivatives for wound healing in rats/mice: Evidence from animal studies and insight into molecular mechanisms. Int Wound J 2024; 21.

[32]. Pertiwi RD, Kristanto J, Praptiwi GA. Uji aktivitas antibakteri formulasi gel untuk sariawan dari ekstrak daun saga (Abrus precatorius Linn.) terhadap bakteri Staphylococcus aureus. JIM 2016; 2: 239–47.
[33]. Riskayanti NP, Radithia D, Maharani A. Effect of freeze-dried platelet-rich plasma on FGF-2 and type I collagen expression in traumatic ulcers of diabetes mellitus: An in vivo study. Dent J 2025; 58: 361–6.
[34]. Sari AP, Anugrah MP, Novita R. Efficacy of Patin (Pangasius sp.) gelatin on macrophage and fibroblast proliferation in traumatic ulcer rats. PJVS 2025; 28: 151–8.
[35]. Kawasaki H, Altieri D, Lu C. Inhibition of apoptosis by survivin predicts shorter survival rates in colorectal cancer. Cancer Res 1998; 58: 5071–4.
[36]. Singer AJ. Healing mechanisms in cutaneous wounds: Tipping the balance. Tissue Eng Part B Rev 2022; 28: 1151–67.
[37]. Pramono A, Mayasari LO. Efektivitas pemberian ekstrak gel belimbing manis (Averrhoa carambola Linn.) terhadap kesembuhan ulkus traumatikus: Studi in vivo terhadap mukosa tikus (strain Wistar. In: Universitas Muhammadiyah Semarang, ed. Prosiding Seminar Nasional Publikasi Hasil-Hasil Penelitian dan Pengabdian Masyarakat. Semarang, 2017.
[38]. Sartika D, Nessa. R, M. Efektivitas salep fraksi n-butanol daun sirih hijau (Piper betle L.) terhadap penyembuhan luka bakar mencit. Medika Saintika 2024; 15: 153–64.
[39]. Supia DR, Yuniartika W. Studi literatur: Perawatan luka bakar grade II dengan delima (Punica granatum. In: Universitas Muhammadiyah Tangerang, ed. Proceeding University Research Colloquium. Tanggerang, 2020.
[40]. Palumpun EF, Wiraguna AAGP, Pangkahila W. Pemberian ekstrak daun sirih (Piper betle) secara topikal meningkatkan ketebalan epidermis, jumlah fibroblas, dan jumlah kolagen dalam proses penyembuhan luka pada tikus jantan galur Wistar (Rattus norvegicus). J E-Biomedik 2017; 5.
[41]. Habsari CR, Graharti R, Sari MI. Efek buah apel (Malus sylvestris Mill.) sebagai pencegahan kerontokan rambut. Medula 2019; 9: 205–11.
[42]. Astuti EJ, Rafikayanti A, Purwanto S. The antioxidant activity comparison of Malus sylvestris Mill and its processed products. FOODSCITECH 2022; 46: 46–52.
[43]. Agung G, Hartini A, Kusumawati PAM. Uji efektivitas ekstrak buah apel manalagi (Malus sylvestris Mill.) konsentrasi 25%, 50%, dan 100% terhadap pertumbuhan bakteri Streptococcus mutans secara in vitro. In: Bali Dental Science & Exhibition. Bali, 2024.
[44]. Noviardi H, Yuningtyas S, Adzani A. Antioxidant and antidiabetic activities of Manalagi apple (Malus sylvestris Mill.) juice and water kefir: An in vitro and in silico study. Trop J Nat Prod Res 2025; 9: 5520–8.
[45]. Fadilah NIM, Phang SJ, Kamaruzaman N. Antioxidant biomaterials in cutaneous wound healing and tissue regeneration: A critical review. Antioxidants 2023; 12:1–35.
[46]. Alberts A, Lungescu IA, Niculescu AG. Natural products for improving soft tissue healing: Mechanisms, innovations, and clinical potential. Pharmaceutics 2025;17.
[47]. Auditto S, Contardi M, Gnocchi C. Harnessing natural compounds and external stimuli for advanced wound healing: A review of combination therapy strategies. J Drug Deliv Sci Technol 2024; 101.
[48]. Roman J. Fibroblasts—Warriors at the intersection of wound healing and disrepair. Biomolecules. 2023; 13: 1–19.
[49]. Kanta J, Zavadakova A, Sticova E. Fibronectin in hyperglycaemia and its potential use in the treatment of diabetic foot ulcers: A review. Int Wound J 2023; 20: 1750–61.
[50]. Podolak I, Grabowska K, Sobolewska D. Saponins as cytotoxic agents: An update. Phytochem Rev 2023; 22: 113–67.
[51]. Aprilia RC. Pengaruh pemberian salep ekstrak ampas apel manalagi (Malus sylvestris Mill.) terhadap ekspresi IL-6 dan jumlah sel radang sebagai penyembuhan luka insisi pada hewan coba tikus (Rattus norvegicus) [Undergraduate Thesis]. Universitas Brawijaya; 2018.