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Betel Leaf Extract Efficacy on Wound Healing: A Systematic review

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ABSTRACT
Betel leaf extract effectively accelerates wound healing, apart out of the low risk of side effects, is economically affordable and readily available in the surrounding environment.
To identify the potency of betel leaf extract in the inflammatory phase, proliferation and remodeling of wound healing phases
Literature quest: PubMed, EBSCO host, Proquest, Science Direct, DOAJ and GARUDA. Published in the last ten years, RCT approach, full text, in English and Bahasa version
As many as five articles were reviewed, affecting the inflammatory phase, the proliferative phase and as an antibacterial agent that ultimately affects the maturation phase. In acute wounds, the IL-1β content was statistically correlated with the betel leaf extract treatment group at a concentration of 3% ($\rho < 0.002$, $r = 0.701$) which affected inflammation. In diabetes mellitus (DM) ulcers, blood vessel growth and increased collagen layer thickening affect cell proliferation, increased epithelialization, more melanin, melanocyte and fibrous tissue formation ($\rho<0.05$), increased granulation tissue weight on the third and seventh post wound making ($\rho<0.05$), hydroxyproline content increased significantly ($\rho<0.05$), increased levels of superoxide dismutase (SOD) ($\rho<0.05$), there was a significant decrease in malondialdehyde (MDA) ($\rho<0.05$), epidermal thickening, more lots of fibroblasts and few macrophages, and effective in inhibiting bacterial growth ($\rho<0.05$), giving betel leaf extract 5% healing time: 6.00 days ± 0.71 and Staphylococcus aureus bacteria: 1st rep: positive and 2nd repetition up to repetitions 3rd: negative (no longer available), and topical application of betel leaf extract can accelerate the wound healing process in 10.80 days ± 0.422.
Betel leaf extract has the potential to heal wounds both acute wounds, infection wounds and diabetic ulcers.

Keywords: Wound, Betel leaf extract, Wound Healing

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BACKGROUND

The prevalence of chronic wounds globally is revealed to be 221 cases in 1000 population (Laura Martinengo, Maja Olsson, 2019). Europe is estimated as many as 1.5-2 million people gain acute and chronic wounds (Christina L, Richard S, 2016). The crude incidence rate (CIR) in Asia in 2017 was estimated at 15 in 100,000 vein wounds, 56 arterial wounds, 168 diabetic wounds and 183 as pressure wounds (Orlanda Q Goh, Ganga Ganesan, 2020). In 2018, Basic Health Research stated that 9.2% or 1,017,290 people have wounds (Kemenkes RI, 2018). With the number of wounded patients, betel leaf extract is an option in accelerating wound healing apart from its availability in the surrounding environment which is indeed convenient to gain.

Betel leaf is a type of medicinal plant with properties in healing wounds, widely spread throughout Indonesia (Aliefia Ditha Kusumawardhani, 2015). Betel leaf contains eugenol, estragole, linalool, α-copaene, anethole, chavicol, and caryophyllene, which practicality as antibacterial agents for mycobacterium smegmatis, staphylococcus aureus and pseudomonas aeruginosa (Mitali Madhumita, Proshanta Guha, 2019). Furthermore, it may support expedite the recuperation process of acute wounds, chronic wounds, infectious wounds and wounds with co morbid diseases, which are related to anti-bacterial (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017), angiogenesis (Irvanu Dzikri Hasbian Nur, Rini Maya Puspita, 2015) and anti-inflammatory (Fardila, 2018) on betel leaf which is demanded in the wound recuperation fulfillment.

METHODS

Research Design

This systematic review was conducted using the PRISMA 2009 guidelines. PRISMA is an international guide for systematic review articles (Moher D, Shamseer L, 2015).

Searching Strategy

Utilize 6 databases: PubMed, Proquest, Sciencedirect, EBSCO host, DOAJ, and GARUDA, with the following keywords: (Wound AND betel leaf extract AND control OR standard OR conventional OR No intervention wound healing).

Article quality assessment and bias risk assessment

Assess the feasibility of articles using the Critical Appraisal Skill Program (CASP) RCT (CASP, 2018), assess the quality of the Effective Public Health Practice Project (EPHPP) articles (Thomas, Ciliska, Dobbins, & Micucci, 2004) and assess the risk of bias based on the Cochrane Risk of Bias Tool (Julian P.T. Higgins et al., 2011).

Data extraction and management

Data extraction through reviewed articles that met the inclusion criteria was then collected: author, year, country, title, method, objective, participant, length of study, instrument, intervention, outcome and article result. Finally, a description of the data handling method and study results.

Ethical Consideration

Ethic clearance was obtained by the Ethics Committee of the Hasanuddin University Medical Faculty with the Ethical Approval Recommendation Number: 16 / UN4.6.4.5.31 / PP36 / 2021.

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RESULTS

Study Selection

361 articles were successfully obtained based on screening results in 6 databases. A total of 44 articles indicated duplication, 279 articles were not relevant to the research question, 8 articles were not in English or Indonesian, 25 articles were not full text and 1 article was not RCT. The final result is 5 articles which are then carried out by grid synthesis (Tabel.1).

Research Design

Based on the 5 articles reviewed, there are 2 published articles nationally (Muhammad Zuhdan, 2014) and (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017), as well as 3 internationally published articles (Kiran C Nilugal, 2014), (Maryunis, 2016), (Nur Amalina Ghazali, Azree Elmy, 2016). 2 articles from Malaysia (Kiran C Nilugal, 2014) and (Nur Amalina Ghazali, Azree Elmy, 2016) and 3 articles from Indonesia (Maryunis, 2016), (Muhammad Zuhdan, 2014), and (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017) .

Assessment of study feasibility and risk of bias in research

All studies are feasible and approved by the authors and two co-authors. In the CASP RCT design (CASP, 2018), all articles were found, valid, reliable and applicable, focused on research problems, randomized intervention was carried out, all experimental animals were involved in the research and were taken into account Until the end of the study, the characteristics of the experimental animals were the same from the initial phase of the study, both the control group and the intervention group were treated equally, the intervention effect was reported comprehensively, the intervention effect was reported, the benefits were proportional to the costs used and the study results were applicable (Table. 2). For study quality (Table 3), 5 studies had a low risk of bias (Muhammad Zuhdan, 2014), (Kiran C Nilugal, 2014), (Maryunis, 2016), (Nur Amalina Ghazali, Azree Elmy, 2016)(Rissa Laila Vifta, Muhammad Andri Wansyah, 2017). Meanwhile, the assessment of the quality of the EPHPP study (Table 4) concluded that all 5 studies had strong qualities.

Sample

All studies used experimental animals, consisting of 30 male white rats (Muhammad Zuhdan, 2014), 20 adult female wistar albino rats (Kiran C Nilugal, 2014), 72 experimental rats (Maryunis, 2016), 64 Sprague- male dawley (Nur Amalina Ghazali, Azree Elmy, 2016) and 25 male Wistar rats (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017). The highest sample was 72 white rats (Maryunis, 2016) and the sample of at least 20 adult female wistar albino rats (Kiran C Nilugal, 2014).

Topical Types of Betel Leaf Extract

Seluruh studi memakai ekstrak daun sirih hijau (*piper betpe leaf*) yang dibuat topikal berbentuk krim ada 2artikel yaitu pada penelitian (Maryunis, 2016) dan (Nur Amalina Ghazali, Azree Elmy, 2016) sedangkan yang berbentuk salep ada 3 artikel yaitu (Muhammad Zuhdan, 2014), (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017) dan (Kiran C Nilugal, 2014).

Research Duration

The average length of the study is 7-21 days, the shortest research intervention is for 7 days (Nur Amalina Ghazali, Azree Elmy, 2016) and (Rissa Laila Vifta, Muhammad Andri

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Wansyah, 2017), other studies have 14 days (Muhammad Zuhdan, 2014). While the article with the longest research intervention was 21 days (Kiran C Nilugal, 2014).

Betel Leaf Extract Concentration

Administration of betel leaf extract starts at the lowest concentration of 0.5 mg (Muhammad Zuhdan, 2014) and 50 mg / kg of betel leaf (Nur Amalina Ghazali, Azree Elmy, 2016) while the highest concentration is 10% (Kiran C Nilugal, 2014) and the lowest 2% (Maryunis, 2016).

Duration of Administering Betel Leaf Extract

Based on the duration of giving betel leaf extract, it was obtained once a day in the study (Muhammad Zuhdan, 2014), (Kiran C Nilugal, 2014) and (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017) while giving once every three days in the study (Nur Amalina Ghazali, Azree Elmy, 2016), and (Maryunis, 2016).

Effect of Betel Leaf Extract on Wound Healing Process

1. **Effect on IL- β**

   The concentration of betel leaf extract affects the inflammatory process in the wound, where the normal level of IL-β concentration is <15 pg / ml. On the 3rd day, 2% betel leaf extract: 1.07 picogram / milli liter (pg / ml) ± 0.65 (ρ< 0.060, r = 0.420) and 3% betel leaf extract: 0.97 pg / ml ± 0.46 (ρ< 0.002, r = 0.701), while in the negative control group (Vaseline) 1.49 pg / ml ± 0.93 (ρ< 0.217, r = 0.218), and positive control (Bioplasenton) 1.83 pg / ml ± 0.81 (ρ< 0.249, r = 0.190). On the 7th day the concentration of IL-β in the administration of 2% betel leaf extract: 1.57 pg / ml ± 0.41, 3% betel leaf extract: 1.68 pg / ml ± 0.67, negative control group (vaseline) 1.15 pg / ml ± 0.86, and positive control (bioplasenton) 0.92 pg / ml ± 0.55. On day 14, the concentration of IL-1β was obtained in the administration of 2% betel leaf extract: 2.30 pg / ml ± 1.66, 3% betel leaf extract: 2.58 pg / ml ± 1.05, negative control group (vaseline) 2.67 pg / ml ± 1.71 , and positive control (bioplasenton) 2.11 pg / ml ± 0.70 (Maryunis, 2016). The IL-1β content was statistically correlated with the betel leaf extract treatment group at a concentration of 3% (ρ< 0.002, r = 0.701) (Maryunis, 2016). From these data it can be concluded that, the betel leaf extract treatment group at a concentration of 2%, p value = 0.060 and r value = 0.420, which means there is no correlation between the overall time period (3rd, 7th and 14th) and the content of IL-1β, there is a possibility of decreasing the IL-1β content in the overall time period (3rd, 7th and 14th) in the wound healing process. The betel leaf extract treatment group was at a concentration of 3%, p value = 0.002 and r = 0.701, which means that there is a correlation between the overall time period (3rd, 7th and 14th) and IL-1β content, so there is a possibility an increase in IL-1β content in the overall time period (3rd, 7th and 14th) in the wound healing process, which indicates an inflammatory process right on the administration of 3% betel leaf extract, with a decrease in IL-1β concentration on day 7. -3 is 0.97 pg / ml (Maryunis, 2016).

2. **Effect on wound diameter**

   According to other studies, 10% betel leaf ointment group, (p<0.05): Diameter of wound on day 0: 401.20µm ± 0.83, day 5: 326.06 µm ± 0.82 with a presentation of 15% wound closure, day 10 : 252.46 µm ± 1.93, 35% wound closure, on day 15: 125.30 µm ± 1.61, 65% wound closure and on day 20: 44.70 µm ± 1.55 with a presentation of 85% wound closure. Negative control group: Wound diameter on day 0: 400.80µm ± 0.83, day 5:

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383.02 µm ± 2.05, 5% wound closure, day 10: 352.52 µm ± 2.08, 10% wound closure, day- 15: 221.62 µm ± 1.83, 42% wound closure, and on day 20: 154.60 µm ± 1.14, 60% wound closure. Whereas in the positive control group: wound diameter on day 0: 401.40µm ± 1.14, day 5: 252.20 µm ± 2.34, day 10: 153.30 µm ± 2.17, day 15: 74.50 µm ± 1.54 and day -20: 10.78 µm ± 0.70. The wound diameter on day 5 to day 20 is getting smaller with the percentage of wound closure reaching 85% on day 20 (Kiran C Nilugal, 2014).

3. Effect on histopatological features

Hispatological features in the treatment group showed an increase in the formation of melanin, melanocytes and fibrous tissue, and in the negative control group, the formation of thin epithelialties. So it can be concluded that there was a significant increase in wounds treated with 10% betel leaf ointment where P <0.05, hispatological evaluation there was an inflammatory cell infiltration which was marked by increased formation of blood vessels and an increase in the thickening of the collagen layer which affected cell proliferation, increased epithelialization, more melanin formation. , melanocytes and fibrous tissue (Kiran C Nilugal, 2014). In the DM-PB group on day 3, the weight of granulation tissue was obtained: 1.98mg ± 0.63 and day 7: 3.19mg ± 0.15, while the hydroxypoline level: 0.0092µg / mg ± 0.0016, superoxide dismutase (SOD): 6.82U / ml ± 0.75, and malondialdehyde (MDA): 0.11nmol / mg ± 0.63. Control group day 3: 2.86mg ± 0.13, day 7: 3.85mg ± 0.13, and hydroxypoline level: 0.0073µg / mg ± 0.0013, SOD: 3.12U / ml ± 0.12, MDA: 0.08nmol / mg ± 0.67 . Control DM group day 3: 1.51mg ± 0.85, and day 7: 2.04mg ± 0.19, with a hydroxypoline level: 0.0186µg / mg ± 0.0017, SOD: 2.15U / ml ± 0.84, MDA: 0.17nmol / mg ± 0.58. Group DM SN day 3: 2.66mg ± 0.56, day 7: 3.72mg ± 0.14, and hydroxypoline level: 0.0087µg / mg ± 0.0013, SOD: 4.57U / ml ± 0.36, MDA: 0.15nmol / mg ± 0.79. The conclusion is that there is a significant difference (P <0.05) in the granulation tissue between the control DM group and the DM-PB given betel leaf extract on DM-PB increased granulation tissue weight on the 3rd and 7th day after wound making. The hydroxyproline content increased significantly (P <0.05), increased levels of SOD (p <0.05). In the proliferation phase, there was a significant decrease in MDA (P <0.05). There was keratin deposition and epidermal thickening, epidermal invagination with reepitalization, more fibroblasts and less macrophages, increased collagen fiber deposition (microscopic) (Nur Amalina Ghazali, Azree Elmy, 2016).

4. Effect on Wound Healing Duration

The progress of wound healing appeared to be faster where the mean duration of healing of wounds in the test animals in three groups was analyzed using Oneway Anova, the value of p<0.05 was obtained, based on the Oneway Anova test, it was found that the application of betel leaf extract ointment can accelerate the healing process of wounds in 10.80 days. ± 0.422 compared to using povidone iodine: 11.9 days ± 0.316; and Vaseline album: 13.8 days ± 0.422 (Muhammad Zuhdan, 2014). Provision of 3% betel leaf extract, healing time: 7.00 days ± 0.71, 4% betel leaf extract healing time: 6.20 days ± 0.84, betel leaf extract 5% healing time: 6.00 days ± 0.71. In negative control group, wound healing time: 9.00 days ± 0.71, positive control group wound healing time: 5.80 days ± 0.84. 4% and 5% betel leaf extract provides healing on average 6 days faster than 3% betel leaf extract (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017). Compared with vaseline and bioplasenton treatment, 3% betel leaf extract treatment can improve

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the wound healing process based on ascending time on day 3, day 7 and day 14 (Maryunis, 2016).

5. Effect on the Bacterial

Applying 3% betel leaf extract, Stapylococus aureus bacteria: 1st repetition to 3rd repetition: positive (still present). Betel leaf extract 4% administration of Stapylococus aureus bacteria: Reps 1 to 3: positive (still present). In the administration of 5% betel leaf extract (P = 0.000), Stapylococus aureus bacteria: 1st repetition: positive and 2nd repetition to 3rd repetition: negative (no longer available). In the negative control group, Stapylococus aureus bacteria: 1st to 3rd repetitions: positive and the positive control group, Stapylococus aureus bacteria: 1st to 3rd repetitions: negative due to antibiotics. In phytochemical screening: Betel leaf ethanol extract contains flavonoids, saponins, and tannins. The 5% concentration of betel leaf extract can inhibit bacterial growth optimally with the assumption that MIC is seen at 5% negative bacteria concentrations in the 2nd and 3rd reps (Rissa Laila Vifta, Muhammad Andri Wansyah, 2017).

DISCUSSION

The least research sample was 20 adult female wistar albino rats and the highest sample was 72 rats. This is in accordance with the previous theory that research must have an adequate sample size, relative to the objectives and possible variability of the study, the larger the sample, the greater the population representation (Alwi, 2012). The sample must be 'large enough' so that the effect of the expected magnitude of scientific significance is also statistically significant and if the sample is heterogeneous (Winarsunu, 2017). The research sample should not be 'too large' where the influence of small scientific importance can be detected statistically and the nature of the sample is homogeneous (Winarsunu, 2017). In addition, sample size is important for economic reasons: Small studies can be a waste of resources because they may not provide useful results while large studies use more resources than necessary (KP Suresh and S Chandrashekara, 2012). In experiments involving human or animal subjects, sample size is a critical ethical issue (KP Suresh and S Chandrashekara, 2012). This shows that it is necessary to manage the number of samples to be studied so that the risk of bias and the quality of the research will be better.

Length of study and duration of intervention

The duration of giving betel leaf extract once per day is up to thirds of a day and the length of the study is seven days to 21 days. Giving betel leaf extract is carried out in the first 24 hours and every three days which is expected to stimulate the balance of the inflammatory process, affecting the proliferation of the healing flow can be started to repair the defect, this complex process combines angiogenesis, granulation tissue formation, collagen deposition, epithelialization and wound retraction. that happened simultaneously (Alistair Young, 2011). The duration of treatment is adjusted to the length of the wound healing phase where on days 7 to 21, the wound begins to contract mainly mediated by myofibroblasts, the interaction between actins and myosin pulls the cell bodies closer equally thereby reducing the area of tissue that needs to be healed (Alistair Young, 2011).

Effect of topical administration of betel leaf extract

The results of the identification and evaluation of the effect of betel leaf extract intervention on wound healing, showed the existence of 5 significant articles in accelerating wound healing, with p value <0.005, including: topical administration of betel leaf extract

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as much as 4% and 5% and for betel leaf ointment of 10 % effective in wound healing. The concentration of betel leaf extract can affect the wound healing process in both the inflammatory and proliferation phases so that the maturation phase can be achieved properly, given the correlation between betel leaf containing antioxidant properties and biological activity in the inflammatory process (Vandana Dwivedi, 2014). Acute wounds and chronic wounds that experience an inflammatory process contain macrophages derived from inactive blood monocytes, where chronic wound conditions increase the expression of pro-inflammatory markers IL-1β, MMP-9, TNF-a, and decrease the expression of non-prohealing markers (Rita E Mirza, 2013). Betel leaf extract statistically significant showed the effect of maximum anti-inflammatory activity depending on the dose ($p < 0.05$), to be precise at a dose of 200 mg / kg (66.66% inhibition) (Badrul Alam, 2013). Giving the maximum concentration of betel leaf extract can affect the inflammatory process in the wound, inhibit repetition and on time, besides that topical cream can help moisture in the area of inflammation and help accelerate the penetration of betel leaf extract into the wound (Debjit B, Harish G, 2012).

Betel leaf extract accelerates the proliferation process by increasing blood vessels and increasing the thickening of the collagen layer which affects cell proliferation, increases epithelialization, increases the formation of melanin, melanocytes and fibrous tissue, besides flavonoids affect the decrease in markers of oxidative stress (SOD, MDA and lipid peroxidation) and reduce 11ß HSD-1 enzyme which supports increase the proliferation of keratinocytes and fibroblasts. In the proliferation process, showed that betel leaf extract in methanol increased NIH3T3 cell proliferation and increased wound healing in vitroandin vivi with burn and excision wound models (Le Thi Lien, 2015). NIH3T3 fibroblasts play an important role in the wound healing process through synthesize and secrete skin collagen, newly formed collagen may fill tissue damage, provide a scaffold for epidermal cell migration, and regulate cell migration and proliferation, including promoting epithelial regeneration by forming fibrin substrates and fibronectin (Xiaowen Su, 2017). Betel leaf extract acts as a protective agent in the initial phase of wound healing by increasing the total protein content and the rate of wound contraction (Keat EC, 2010). The wound contraction rate in group III (35.03 +/- 2.96) was higher than that in group II (18.40 +/- 3.87) with $p = 0.014$, and the total protein content in group III was 106.39 +/- 4.46 compared to group II (72.86 +/- 12.86) with $p = 0.050$ so it can be concluded that betel leaf extract acts as a protective agent in the initial phase of wound healing by increasing the total protein content and the rate of wound contraction (Keat EC, 2010).

Betel leaf extract also functions as an antibacterial with a higher concentration which can inhibit bacterial growth and may exterminate the stapylococus aureus bacteria. Menurut (Rodiah rahmawati L, 2020) The content of betel leaf extract can inhibit the growth of Stapylococus aureus which shows that betel leaf extract with a concentration of 0.5%, 1%, 1.5%, 2%, 2.5%, and 3% forms a clear zone around the draw well which means there is no activity of bacteria. The ethanol of betel leaf extraction shows a maximum inhibition zone of 20.2 mm against Escherichia coli which is very close to the 20.6 mm inhibition zone recorded in the standard antibiotic imipenem 10µg / disc, a synergistic antibacterial activity study shows that the ethanol extract of the combination of betel leaf and imipenem records a zone The higher inhibition of 24.3 mm against Pseudomonas aeruginos followed by an inhibition zone of 23.4 mm in the betel leaf ethanol extract + oxacillin against Staphylococcus aureus, this concludes that the betel leaf ethanol extract has a fairly high antibacterial activity (S Saranya, 2020). The minimum inhibitory concentration (MIC) ranged from 0.625% (w / v) to 0.75% (w / v), and the ethanol extract of betel leaf showed

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the highest MIC value for E. coli ATCC 25922 (0.625 mm), Vibrio cholera ATCC 6395 (0.625 mm), and Staphylococcus aureus ATCC 25923 (0.625 mm), it was revealed that the antibacterial activity was highest at around neutral pH and moderate temperature, in order that betel leaf ethanol extract has the potential to be applied as antibacterial (M.Mahfuzul Hoque, 2011).

The two topical types of betel leaf extract in the current review are all effective in wound healing. Betel leaf extract ointment has great stability in the form of a delicate preparation, simple, safe for skin, maintain skin moisture, and more attractive appearance (Grace, Paulina, 2012), In addition, the ointment also releases extracts within one hour of contact with moisture and is easily applied to wounds (Michael Neidrauer,Utku K. Ercan, 2014). The use of topical creams is hassle-free and the shape is softer than ointments making it more comfortable for the patient (Mithun Vishwanath K Patil, Amit D Kandhare, 2012), Cream retains moisture longer and absorbs the extract into the wound more quickly because the external phase in the form of the water phase will dissolve by itself, has a good adhesion test and excellent dispersibility (Utari, unique, 2019).

The limitations on purvey this systematic review including limitedness of the articles and some articles irrelevant to the research question. Limitations of international articles regarding betel leaf extract lead to the searching articles in National journals. There has been no specific systematic review on betel leaf extract on wound healing, grounded the author tries to initiate this systematic review. Future study may pursue current study both in a review and in original research in order that it might be used as evidence based on special wound care using betel leaf extract.

All articles use the RCT design, and to the best of our knowledge this review is the first to be conducted on the effect of betel leaf extract on wound healing.

CONCLUSIONS

Green betel leaf extract (piper betel leaf) in a concentration of 0.5 mg to 50 mg or a content of 2% to 10% betel leaf extract, is effective in the wound healing process, especially in influencing the inflammatory process and the proliferation and antibacterial processes. Topical preparations are in the form of creams and ointments which have the function of accelerating the penetration of substances present in the betel leaf, as a moisturizer for wounds, and are easy to apply to wounds, so that these two topical can be applied according to the conditions and conditions of the wound. Topical administration of betel leaf extract can be given once a day or it can be every three days; this is also adjusted to the condition of the wound. Topical betel leaf extract can be recommended as a complementary herbal therapy in wound care for both acute wounds and wounds with DM, since it is effective in healing wounds ranging from the inflammatory phase, the proliferation phase to the maturation phase in a timely or even faster manner

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CONFLICT OF INTEREST

The researcher state that there is no conflict of interest

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