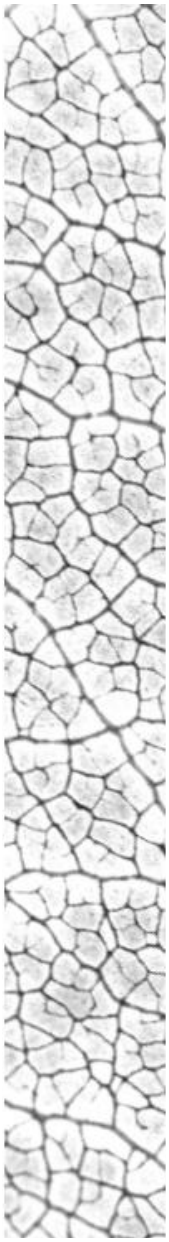

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Ficus deltoidea leaves methanol extract promote wound healing activity in mice

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Abstract
Wound healing is a normal process in skin tissue in response to injury. *Ficus deltoidea* leaves contain phytochemicals, which can play a role in wound healing. This study aimed to assess the wound healing activity of methanol extract of *Ficus deltoidea* leaves on artificial wounds in mice. In total 28 mice (2-3 months old, 20-30 g in weight) were randomly distributed into 7 treatment groups namely group I without treatment (negative control), group II were given povidone iodine 10% (positive control), group III was given a basic ointment and group IV-VII was treated with methanolic extract of *Ficus deltoidea* leaves with concentrations of 20, 40, 60 and 80% respectively. In all test animals, the wound was made with a length of 1 cm, and applied to the treatment according to the group, twice a day for 15 days. At the end of the treatment, wound healing activities were determined by measuring the percentage of wound contractions, Hydroxyproline estimates, and total new tissue DNA. Studies showed that the methanol extract of *Ficus deltoidea* leaves was able to heal wounds starting at a concentration of 20%. Mice treated with 80% extract resulted in the highest DNA and hydroxyproline content. The higher the concentration of the extract, the greater the healing effect of the wound. In summary, methanol extract of *Ficus deltoidea* leaves have potential for wound healing in mice.

Keywords: *Ficus deltoidea* leaves, wound healing, phytochemicals

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INTRODUCTION

Wounds are injuries to parts of the body, namely the loss or damage of a portion of body tissue (Das 2018, Mitzzy et al. 2019). Wounds are also defined as physical damage resulting from the opening or destruction of the skin which can cause an imbalance of function and normal anatomy of the skin (Nagori and Solanki 2011). Wounds can be caused by several factors, including, among others, sharp or blunt trauma, explosions, chemicals, temperature changes, electric shock, animal bites. Wounds result in the opening of the skin as one of the body's defense systems, which results in bleeding as well as the opening of entry points for bacteria, fungi, viruses into the body and also cause inflammation and need to be healed properly.

Wound healing is a biological process that occurs in the body and a complex process that involves continuous interaction between cells and cells and between cells and matrices summarized in three overlapping phases. Three phases of the wound healing mechanism that occur is the inflammatory phase (0-3 days), the proliferation and tissue formation phase (3-14 days) (Reddy et al. 2012, Che Hamzah et al. 2019, Scapagnini et al. 2019) and the tissue remodeling phase (can begin on the 8th day and last until with 1 year) (George Broughton et al. 2006). The goal of wound management is healing wounds in the shortest possible time, minimizing tissue damage, providing adequate tissue perfusion and oxygenation, and getting proper nutrition for wound tissue. Treatment of wounds aims to reduce risk factors that inhibit wound healing, speed up the healing process and reduce the incidence of infected wounds.

The speed of wound healing can be influenced by the substances contained in the drug given, if the drug has the ability to improve healing by stimulating faster growth

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of new cells in the skin, the healing process will be fast. A number of studies showed that traditional plants have the potential to be wound healing agents in addition to chemical treatments (Derakhshanfar et al. 2019, Nugroho et al. 2019; Fallah et al. 2019). The use of traditional medicinal plants for wound healing is based on the potential for antiseptic, astringent, anti-inflammatory, antioxidant and antibacterial. Based on previous studies it has been shown that *F. deltoidea* has several pharmacologies effect including antimicrobial (Jain et al. 2006), antinociceptive (Schulz et al. 2003), antioxidant (Nie et al. 2002, Abrahim et al. 2018) as well as anti-inflammatory (Zakaria et al. 2012, Jamaluddin et al. 2019; Samimi et al. 2020). However, studies on *F. deltoidea* for wound healing have not been widely studied. Therefore, this study examined the effect of *F. deltoidea* methanol extract on the wound healing by measuring the percentage of wound contractions, hydroxyproline estimation, and total DNA in new tissue.

MATERIALS AND METHODS

Plant material and methanol extract of *F. deltoidea* leaves were obtained in the welcome area of Samarinda, East Kalimantan, Indonesia. The *F. deltoidea* leaf was washed and then dried. The dried leaves are blended and extracted using the maceration method using 95% methanol solvent. Samples that have been soaked with 95% methanol solvent were stirred every day for 3 days, then filtered. The *F. deltoidea* leaf filtrate was evaporated using a rotary evaporator with heating of 34-40ºC so that the barito leaf paste extract was obtained. The *F. deltoidea* leaf paste extract obtained was then put into ointment pots and stored in the freezer and ready to be used for testing.

Work procedures

Sample preparation and test animals

The test animals used were 28 male mice (*Mus musculus*) aged ± 3 months who were healthy with an average body weight of 20-30 grams. We followed the ARRIVE (Animal Research: Reporting of In vivo Experiments) as a guideline for conducting research with the animal. Male mice were acclimatized for 7 days with pellet feed and drink in ad libitum. The male mice were divided into 7 groups, namely group I mice without treatment, group II positive control (povide iodine), group III placebo mice (base ointment), group IV-VII mice with treatment (base ointment + extract 20, 40, 60, and 80%), where each group consisted of 5 male mice.

Ointment preparation

The preparation of the basic ingredients of the ointment was to be used as the base of the ointment in the form of Vaseline. Preparation of *F. deltoidea* sow leaf extract ointment which was weighed and inserted *F. deltoidea* sow leaf extract into a container with a concentration of 20, 40, 60 and 80% and then put in the ointment. After each was inserted, stirred using spatula until extract and vaseline homogeneous. Then stored in the freezer and ready for use for testing.

Mice treatment

Before treatment, the hair around the back was shaved and the skin was smeared with alcohol. Anesthesia was done by preparing ketamine 2% in advance. Then injected into the area to be wounded in each sample of male mice, while anesthesia using chloroform by absorbing a little chloroform on cotton, then placed a few seconds on the nose of the mouse until fainting. Then make a 1 cm incision with ± 1 mm depth using a sterile scalpel to reach the hypodermic layer. The administration of *F. deltoidea* leaf extract ointment was done by applying it to the wound in mice by using a spatula every day in the morning, from day 1 until the wound was closed after wound cuts. Mice treated and control mice were observed for wound closure every day for 15 days using a caliper and documentation was carried out on the wound using a digital camera.

Estimation of hydroxyproline

In the end of the treatment, a small amount of skin from the new skin was collected and analyzed for the content of hydroxyproline which the basic ingredient of collagen. The skin tissue was dried with hot air in the oven at a temperature of 60-70ºC to a constant weight and hydrolyzed with 6 N HCl at 130oC for 4 hours in a closed tube. Hydrolysate was neutralized until pH 7 was oxidized with Chloramine T for 20 minutes, the reaction was stopped with the addition of 0.4M perchloric acid and the emerging color was intensified with the help of Ehrlich reagent at 60^0C and measured at 557 nm using UV/Vis spectrophotometer (Shimadzu).

Total DNA

The total DNA content was measured from the tissue of wounded mice and smeared with *F. deltoidea* sow extract for 3 days and the sample was taken on day 4. The tissue was processed and extracted using the chloroform-isoamyl alcohol method. The total amount of DNA content in each sample was measured by the number of triplicates using Qubit 4 fluorometer (Thermo fisher scientific).

Data analysis

Measurement data were tested by Statistical Packed Social and Science (SPSS) 22 using the Distribution normality test, the data considered normal if $p > 0.05$. Normal data were analyzed by analysis of variance (ANOVA) and LSD further testing.

RESULTS AND DISCUSSION

Incision wound is a type of wound caused by incisions of sharp objects can be metal or wood. In this research the test animals were used to use a glazed knife and the incision wound length was measured using

Table 1. Effects of *Tabat barito* leaves methanol extract on excisional wound model in mice

Day	Group						
	1	2	3	4	5	6	7
0	10±0^{a}	10±0^{a}	10±0^{a}	10±0^{a}	10±0^{a}	10±0^{a}	10±0^{a}
3	8.35±0.22^{ab}	7.27±0.311^{c}	8.17±0.14^{bc}	9.07±0.34^{ab}	9.3±0.28^{a}	8.07±0.53^{bc}	7.92±0.4^{c}
6	7.7±0.2^{a}	6.15±0.43^{bc}	6.67±0.23^{ab}	6.5±0.28^{abc}	7.25±0.29^{ab}	6.77±0.45^{ab}	5.37±0.56^{c}
9	7±0.16^{a}	4.25±0.31^{c}	5.2±0.24^{bc}	5.67±0.22^{b}	5.87±0.3^{ab}	4.85±0.42^{bc}	2.95±0.7^{d}
12	4.35±0.45^{a}	0.35±0.35^{cd}	3.8±0.1^{a}	3.8±0.11^{a}	1.67±0.17^{b}	0.92±0.18^{c}	0.15±0.11^{d}
15	2.12±0.13^{a}	0^{d}	1.4±0.18^{b}	1.1±0.14^{bc}	0.77±0.1^{c}	0.12±0.07^{d}	0^{d}

Group 1: control negative group without treatment. Group 2: control group treated with Povide Iodine. Group 3: control placebo group treated with Vaseline, Group 4: test group treated with 20% extract in Vaseline, Group 5: test group treated with 40% extract in Vaseline, Group 6: test group treated with 60% extract in Vaseline and Group 7: test group treated with 80% extract in Vaseline

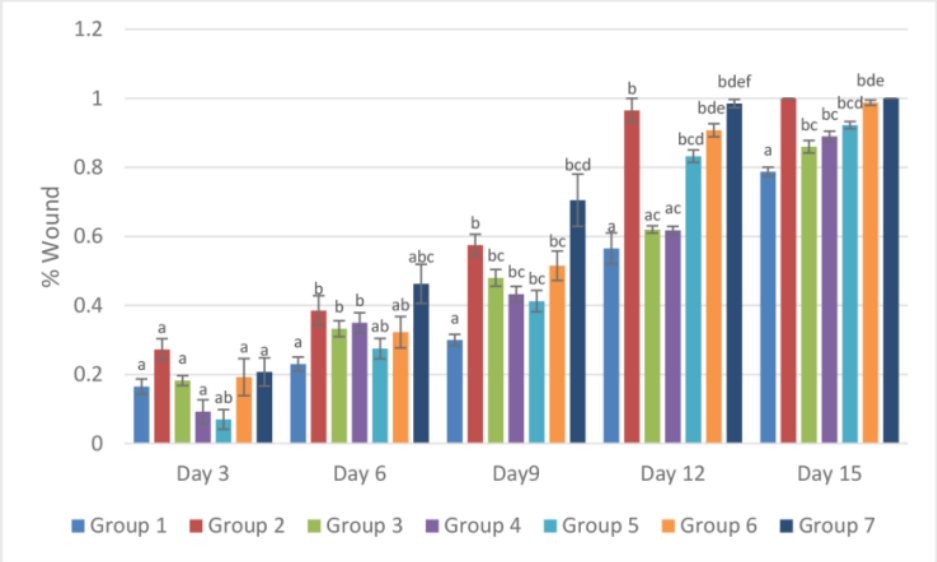

Fig. 1. Effects of *Tabat barito* extract on wound contraction of mice

Group 1: control negative group without treatment. Group 2: control group treated with Povide Iodine. Group 3: control placebo group treated with Vaseline, Group 4: test group treated with 20% extract in Vaseline, Group 5: test group treated with 40% extract in Vaseline, Group 6: test group treated with 60% extract in Vaseline and Group 7: test group treated with 80% extract in Vaseline

a measuring instrument 1 cm long. The wound in the test animal is declared cured by marked changes in the length of the wound that are increasingly shrinking or the percentage of wounds healing larger. This wound model is used to obtain information about the duration of the wound closure after administering the extract compared to the control (Arunachalam and Subhashini 2011, Subhashini and Arunachalam 2011). The objectives of wound management are wound healing in the shortest time, and minimizing tissue damage, thereby reducing the risk factors that can prevent wound healing and lowering the incidence rate of infected wounds. Wound contraction indicates the reduced rate of unhealed areas during treatment so that the wound will close faster if the drug is efficient. By doing proper treatment is expected not only to occur fast healing, but also a proper regeneration process.

The parameters used in macroscopic evaluation for wound healing are visible appearance and measurement of wounds. In this study, the average data progression of the wound size (**Table 1**), increased percentage of wound closure (**Fig. 1**) and photo of wounds (**Fig. 2**) showed the appearance of wound skin. The increase of percentage of wounds closure and biochemical marker tissue such as DNA and hydroxyproline in mice treated with the leaf's methanol extract was significantly better (*P<0.05*) wound enclosure than the control group without the treatment, control of vaseline (**Table 2**).

The results showed that the lowest wound closure was on mice without treatment and base cream. Meanwhile, mice treated with the extract treatment at higher concentration showed the better the wound enclosure especially at 80% which higher than the positive control. The positive control function is as a comparator whether the test substance can be the same effect as the drug used as positive control. The use of povidone iodine as a positive control is based on previous studies, according to (Sammartino et al. 2012) Povidone iodine is an antimicrobial dosage which has bactericidal properties and low toxicity, so the wound can undergo faster healing. However, it appears that the extract treatment causes better wound healing compared to povidone iodine. While the basic ointment (placebo) is still a process of wound healing because the healthy body has a natural ability to protect and restore itself even slower. This is because vaseline can inhibit the loss of water content from skin cells by forming a

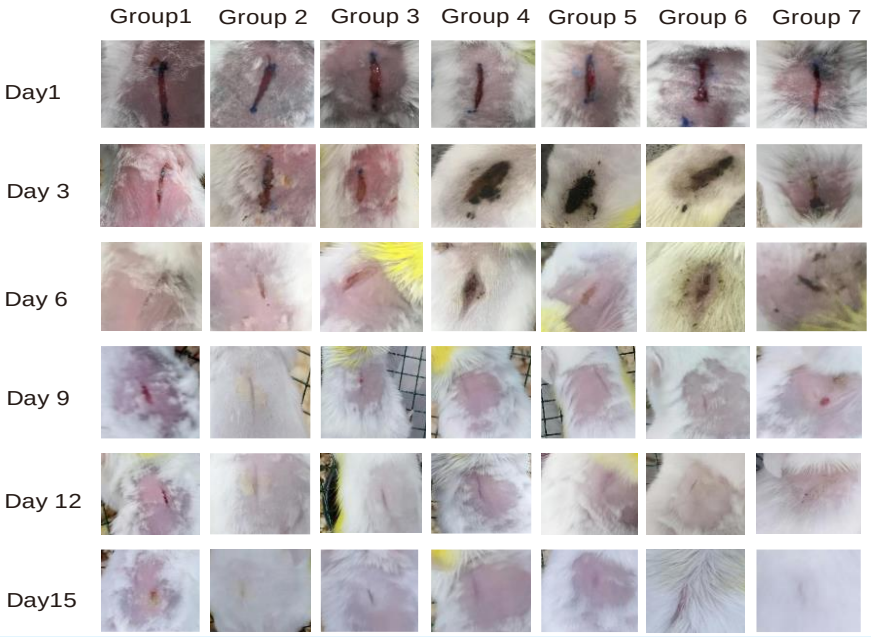

Fig. 2. Wounds condition from mice elucidation on different days
Group 1: control negative group without treatment. Group 2: control group treated with Povide Iodine. Group 3: control placebo group treated with Vaseline, Group 4: test group treated with 20% extract in Vaseline, Group 5: test group treated with 40% extract in Vaseline, Group 6: test group treated with 60% extract in Vaseline and Group 7: test group treated with 80% extract in Vaseline

Table 2. Effect of topical application of *Tabat barito* leaves methanol extract on DNA and Hydroxyproline content of an excision wound

Groups	Total DNA (µg/mL)	Hydroxyproline (mg/g tissue)
1	0,690±0.04^{a}	105.102 ± 22.898^{a}
2	3,427±0.05^{d}	199.672 ± 12.670^{b}
3	1,430±0.14^{b}	133.596 ± 23.961^{b}
4	2,220±0.06^{c}	131.392 ± 12.000^{b}
5	2,257±0.09^{c}	158.220 ± 17.759^{b}
6	2,653±0.04^{c}	161.983 ± 29.960^{b}
7	4,117±0.23^{e}	175.263 ± 24.802^{b}

Group 1: control negative group without treatment. Group 2: control group treated with Povide Iodine. Group 3: control placebo group treated with Vaseline, Group 4: test group treated with 20% extract in Vaseline, Group 5: test group treated with 40% extract in Vaseline, Group 6: test group treated with 60% extract in Vaseline and Group 7: test group treated with 80% extract in Vaseline

waterproff film layer. Control of vaseline base cream serves to find out if the base used has an effect on test animals.

This study showed that the administration of methanolic extracts of *F. deltoidea* leaf may be due to its anti-inflammatory, antioxidant, antibacterial, and analgesic effects (Gupta and Jain 2010). This is because *F. deltoidea* leaf extract has secondary metabolite compounds such as flavonoids, tannins, and saponins that can stimulate collagen formation and can help the wound healing process as it acts as an antioxidant and antimicrobial affects wound connection, and also accelerates epithelization (Senthil et al. 2011, Saroja et al. 2012). A number of previous studies show that the presence of saponins, alkaloids, polyphenols and flavonoids in various parts of the plant may have a wound-healing effect (Sasidharan et al. 2010, Vinothapooshan and Sundar 2010, Anitha et al. 2011, Ekpo et al. 2011). Optimum formula because the content of saponins compounds and flavonoids has been proven to have efficacy as a cleanser and antiseptic that can cure wounds (Saroja et al. 2012), in addition it is known to have antimicrobial effects, and strong antioxidants which is suspected responsible in the wound contraction and the increased velocity of the epidermis tissue epithelization and the infiltration of inflammatory cells in the wound area (Kolasani et al. 2011). The mechanism of action of saponins in wound healing is to stimulate the production of collagen types, which have an important role in the closure of wounds and improve tissue epithelization (MacKay and Miller 2003). According to (Igbinosa et al. 2009) saponins may inhibit microbial growth (bacteriostatic) or kill microbes (bacteriocytes). Saponin works by stimulating the formation of new cells, thereby causing the reproduction and growth of endothelial vascular cells, vascular smooth muscle cells and fibroblasts, thereby causing cellular growth that eventually improves damaged blood vessel. Flavonoids act by inhibiting lipid peroxidation processes (Nayak et al. 2006) and are responsible for scavenging free radicals, (Anitha et al. 2011) thereby preventing and slowing down cell necrosis, and enhancing vascularity in wounds area. Inhibition of lipid peroxidation is believed to enhance the viability of collagen fibrils by enhancing collagen and vascularity, preventing cell damage, and promoting DNA synthesis (Nayak et al. 2006). The use of antioxidants in wound healing is due to the fact that cell proliferation, inflammation suppression, and contractions of the collagenous tissues are inhibiting the existence of free radicals. This high antioxidant activity

can accelerate wound healing as it can stimulate the production of endogenous antioxidants in wound sites and provides an environment conducive to wound healing (Ahmed et al. 2012). While the tannins according to (Robinson 1995) serves as an astringent that can cause the dissolving of skin pores, tighten the skin, stop the exudate and mild bleeding, so as to cover the wound and prevent the usual bleeding on the wound. These results suggested that the methanol extract of *F. deltoidea* is also able to promote collagen synthesis and accelerate the formation of granulation tissues in the final period of wound recovery. (Lanini et all 2019)

Hydroxyproline, the main component of collagen, has been used as a biochemical marker for tissue collagen (James and Victoria 2010). In addition, collagen is the constituent responsible for the growth of tissue healing, which can be measured by estimating the concentration of hydroxyproline. Thus, the higher the concentration of hydroxyproline, the faster the wound healing rate, which is a reflection of increased cell proliferation (DNA) (Roy et al. 2012). Hydroxyproline levels were found to be significantly higher in all extract treatment groups. This clearly indicates that the leaf methanol extract of *F. deltoidea* facilitates the wound healing process. Increased hydroxyproline content of animals treated with extracts enhances the maturation of collagen due to increased cross-linking of collagen fibers (Mukherjee et al. 2013). A significant increase in hydroxyproline content revealed increased migration of fibroblast cells, epithelial cells, and the synthesis of extracellular matrices together with collagen during the healing process on mice treatment. The increased DNA content of the treated wound indicates hyperplasia (blood cell proliferation) (Wang et al. 2011). The DNA content of extracts treated animals also appears significantly higher compared to the negative control groups and Vaselin. This signifies that the *F. deltoidea* leaf methanol extract may have a wound healing effect by means of tissue remodeling, collagen deposition and epithelial repair that leads to proliferation, mobilization, migration and differentiation of new cellular and tissue.

Wound healing occurs mainly in three main processes i.e. epithelium, contraction and build-up of connective tissues. New collagen and subsequent maturation regulate the healing level (Agarwal et al. 2009, Vafaei-Nezhad et al. 2020). In the early process of wound healing, inflammation promotes the migration and proliferation of endothelial cells, which synthesizes extracellular matrices including collagen, and keratinocytes resulting in neovascularization and re-epithelization of the wound tissue (Clark 1991). Epithelization is one of the main phases in the wound healing process, in addition to the formation of granulation tissue with collagen and deposition of connective tissue proteins and angiogenesis. Epithelization which is the process of renewal epithelium, involving proliferation and migration of epithelial cells to the center of wounds and wound contractions caused by the action of myofibroblasts (Mohan 2005). Flavonoids have been demonstrated to increase the migration and proliferation of epithelium cells, the formation of granulation tissues, and increase migration and activity of myofibroblast (Muralidhar et al. 2013). Studies conducted by (Muralidhar et al. 2013) showed that the flavonoids can significantly accelerate the wound healing process by increasing the rate of wound contraction, the decreasing period of epithelization, increasing collagen deposition, and the formation of granulation tissue.

CONCLUSION

The leaf methanol extract *F. deltoidea* potentially as an alternative to wound medication due to the treatment of 80% leaf ethanol extract, indicating the average closure of the length of the wound, the highest DNA and hydroxyproline content.

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