



Literature Review: Effect of Cherry Leaf Extract on Diabetic Wounds

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Abstract. The prevalence of diabetes mellitus (DM) is increasing from year to year. One threat must be watched out for if a DM patient is injured. These wounds can become chronic diabetic wounds where the injury is easily infected or infected with pathogenic bacteria. Since chronic diabetic wounds usually occur on the feet, the most severe risk of this condition is the amputation of the leg. Wound healing can be done by adding traditional ingredients as an alternative treatment, such as cherry leaves. Cherry leaf can potentially be used in wound care because it functions as an antiseptic, anti-inflammatory, and analgesic. The purpose of this study was to examine the effectiveness of cherry leaf in diabetic wound healing. The research method is a literature study. This study uses a literature review method with keywords like *Muntingia calabura* leaves, wound, and diabetic mice. The databases used are Google Scholar, Pubmed, and Science Direct. The results of the search obtained three research articles. The article used is true-experiment research with animal models using mice as experimental animals. Data analysis uses literature selection (PRISMA) with inclusion criteria: manuscripts that can be accessed in full text in the range of years published from 2015- 2022. The feasibility quality assessment uses the JBI Critical appraisal case-control study. The results showed an effect of giving cherry leaf extract on diabetic wound healing. The conclusion is that cherry leaf extract has active compounds that are important in the wound healing process, both acute wounds and chronic wounds, such as diabetic ulcers.

Keywords: *muntingia calabura* · wound · diabetic mice

1 Introduction

Diabetic ulcers are one of the most common and feared complications of Diabetes Mellitus (DM). The incidence of diabetic ulcers is 15% of the total population of type-2 diabetes. In the course of the disease, about 14–24% of diabetic ulcer patients require amputation [1]. It is estimated that 25%-90% of all amputations are associated with diabetes. Diabetic foot amputation tends to increase the risk of death from diabetes over time [2].

Diabetic ulcers require intensive care and a lot of costs, so using traditional medicine to treat diabetic ulcers will significantly help the community [3]. Traditional ingredients

Table 1. PICOST framework

| | |
|--------------|-----------------------------------|
| Population | Diabetic Mice |
| Intervention | Giving cherry leaf extract |
| Comparison | Wound comparison before and after |
| Output | Wound Healing |
| Study | True experiment |
| Time | 2015–2022 |

that can be used as an alternative treatment in wound care are cherry leaves (*Muntingia calabura* L). Cherry leaf is local, easy to plant, widely distributed in Indonesia, and economical [4].

The content possessed by cherry leaves includes tannins, flavonoids, glycosides, and saponins [5]. Flavonoids and tannins can inhibit the growth of *Staphylococcus aureus* bacteria. Flavonoids can be used as antidiabetics because they can lower blood sugar levels. Cherry leaf can potentially be used in wound care because it functions as an antiseptic, anti-inflammatory, and analgesic [6]. The antioxidant content in cherry leaves can accelerate wound healing and regeneration of the skin layer.

2 Methods

The method used in writing this article is a literature review, namely a description of the theory and research obtained from summary reviews and analysis based on several databases with topics tailored to the study. Inclusion criteria: accessed from the database, subjects were mice with diabetic wounds, full-text script, the languages used were English and Indonesian, published from 2015 to 2022, according to the research topic, namely the effectiveness of giving cherry leaves on wound healing in diabetic mice (Table 1).

Exclusion criteria: manuscripts in abstract or inaccessible form, articles not by the research topic, incomplete articles. Articles were selected using PRISMA literature selection. And after that, critical appraisal tools were analyzed using the Joanna Briggs Institute (JBI) case-control study. The number of articles that deserve to be reviewed in this study is three articles. The process of searching and reviewing the literature can be seen in the diagram below (Fig. 1).

3 Results and Discussion

The search results for journal articles through Pubmed, Google Scholar, and Science Direct were carried out on October 8, 2022; in the 2015–2022 range, 253 journals were found that matched keywords. Furthermore, screening was carried out through titles, and three journal articles passed the critical appraisal tools assessment using the Joanna Briggs Institute (JBI): a case-control study. Articles are declared eligible if the check scores more than 5 (Table 2).

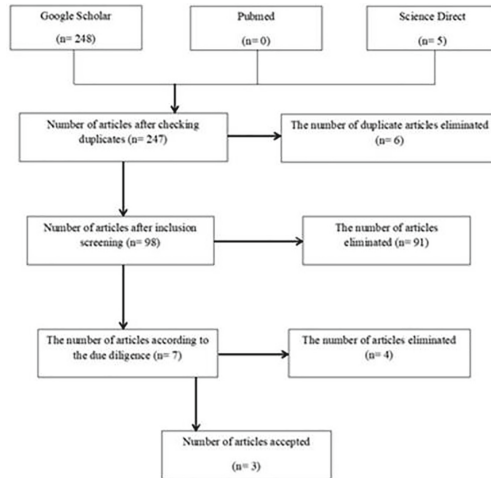


Fig. 1. Search results review

Based on the three articles analyzed, several subtopics were obtained, namely:

A. *Making cherry leaf extract*

When used as an alternative to topical treatment, the method of making cherry leaf extract can be done as an ointment/ointment [7] or gel [10]. The manufacture of cherry leaf extract begins with drying cherry leaves without exposure to the sun. The dried cherry leaves are then blended to make a fine powder. The powder was extracted using 96% ethanol and filtered using filter paper; then, the results were mixed using vaseline and different concentrations of 30%, 40%, and 50 [7].

Another method of making ethanol extract from cherry leaves is by maceration method with 4,000 ml of 70% ethanol as solvent. Three hundred grams of dried cherry leaf powder was put into a glass container, soaked with 70% ethanol solvent for 24 h, and stirred as often as possible. The simplicia was macerated using a macerator for 3 h. After maceration, it was allowed to stand for 3 h to be precipitated, and the macerate was taken. After the simplicia was silenced, it was vacuumed using a vacuum. The macerate is in the form of a liquid extract which is then evaporated using a rotary evaporator to obtain a slightly thick extract. The cherry leaf extract was evaporated again in a water bath, and a very concentrated blackish-green thick extract was obtained [11]. Preparation of ethanol extract of cherry leaf ointment mixed with vaseline flavum with a total weight of 1 g used for two days of use, partially mixed with ethanol extract of cherry leaf, then added the remaining Vaseline flavum, stirred again until everything is mixed or homogeneous.

B. *Manufacture of diabetic animal models*

The animal models used were white male mice, aged 8–12 weeks, healthy, each weighing 20–25 g, six for each treatment, with a total of 24 animals. Mice were acclimatized in advance for one week. Furthermore, blood checks were carried out where one drop of blood was taken from the tail, which was examined using StripTest before

Table 2. Extraction of Article Researches

| Title | Author & Year | Research purposes | Methods | Outcome |
|--|--|--|---|---|
| Kersen leaf extract ointment decreases blood sugar levels and migration of polymorphonuclear cells in hyperglycemic mice | Ginting, Jayawardhita, & Dharmawan; 2021 [7] | To determine the effect of cherry leaf extract ointment on blood glucose levels and the number of polymorphonuclear cells | The research object used 24 hyperglycemic mice (<i>Mus musculus</i>) with alloxan-induced at a dose of 150 mg/kgBW, then an incision was made and treated with ethanol extract of cherry leaf ointment at concentrations of 30%, 40%, and 50% in mouse incisions. Then measured, blood glucose levels and the number of polymorphonuclear cells observed through a microscope | Cherry leaf extract ointment with concentrations of 30%, 40%, and 50% affected decreasing blood glucose levels; with concentrations of 40% and 50% topically, it involved reducing migration of polymorphonuclear cells (PMN). |
| Based on signs of inflammation and the presence of scabs, leaf extract of <i>Muntingia calabura</i> ointment accelerate the healing of incision wound in hyperglycemic mice | Kewuta, Dada, & Jayawardhita; 2021 [8] | To determine the speed of healing of incision wounds in hyperglycemic mice, we used cherry leaf extract ointment (<i>Muntingia calabura</i> L), which contains compounds that can accelerate wound healing. | This study used 24 mice that were induced with alloxan so that the mice experienced hyperglycemia and then performed a skin incision on the back. The mice were then given four treatments of cherry leaf extract ointment (0%, 30%, 40%, 50%) and observed wound healing (signs of inflammation and scabs) for five days. | There was a significant difference from the control treatment (0%), with the treatment of 30% and 40% both seen from the presence of signs of inflammation and scabs. This study shows that cherry leaf extract ointment with a concentration of 30-40% accelerates wound healing |

(continued)

Table 2. (continued)

| Title | Author & Year | Research purposes | Methods | Outcome |
|--|-------------------------------------|--|---|---|
| Kersen leaf extract ointment is effective in increasing the angiogenesis process on skin incision wound healing of hyperglycemia mice | Nadira, Jayawardhita, Adi; 2021 [9] | This study aimed to determine the effect of giving cherry leaf extract ointment on the acceleration of wound healing in mice with hyperglycemia by observing the angiogenesis process. | This study used 24 male mice (<i>Mus musculus</i>) as experimental animals, which were divided into four treatment groups, (T0) with 0% cherry leaf extract concentration, (T1) 30%, (T2) 40%, and (T3) 50%. Mice were induced using alloxan (150 mg/kg BW, intraperitoneally) for hyperglycemia, then incised on the back with a wound length of ± 1.5 cm and a depth of ± 2 mm to reach the subcutaneous tissue. Then treated using cherry leaf extract ointment topically for five days, then biopsied on the 6th day. The wound healing process was observed on histopathological preparations based on angiogenesis results, and then the average number of blood vessels was calculated for each treatment. | The results obtained were that the administration of cherry leaf extract ointment on the skin incision of hyperglycemic mice was proven to increase the angiogenesis process, as seen from the comparison of the average number of blood vessels between the four treatment groups. It can be concluded that the concentration of 50% cherry leaf extract has been shown to have a higher mean number of blood vessels resulting from the angiogenesis process compared to concentrations of 0%, 30%, and 40% so that it can accelerate the healing process of skin incision wounds in mice with hyperglycemia. |

and after injection of Alloxan (Sigma Aldrich, St. Louis, USA) as much as 150 mg/kg BW intraperitoneally, then observed for three days. Mice that were declared to have experienced hyperglycemia were injected with an anaesthetic with Ketamine as much as 50 mg/kg BW, then an incision was made using a scalpel on the skin on the back with a wound length of ± 1.5 cm and a depth of ± 2 mm to reach the subcutaneous tissue. In the incisions, the cherry leaf extract ointment is applied topically with different

concentrations (0%, 30%, 40%, and 50%) for five days, two times a day. On the 6th day, a biopsy was performed with the administration of anaesthesia first using Ketamine [8].

C. *Making histopathological preparations*

A mice skin biopsy was performed for histopathological preparation. A skin biopsy of each mouse was performed using sterile surgical scissors first, and then a skin preparation measuring 1.5 x 1.5 cm was taken. The cut skin samples were fixed by placing them in four pots containing 10% formalin solution to be separated according to treatment (Cherry leaf extract ointment with concentrations of 0%, 30%, 40%, and 50%). The biopsy results are made into histopathological preparations for microscopic examination [9].

D. *Benefits of cherry leaf extract on wound healing*

E. *Reducing signs of inflammation, scab, and wound diameter*

The wound healing process can be measured by scoring the signs of inflammation and scab in experimental animals. The results showed significant differences between the four treatments, namely cherry leaf extract with concentrations of 0%, 30%, 40%, and 50%.

Giving cherry leaf extract ointment concentrations of 30% and 40% was more effective in accelerating the healing of diabetic mice incision wounds [8]. Research conducted by Handayani & Sentat [11] showed that the most effective dose of cherry leaf ethanol extract for healing burns was 10.4 mg, with a healing percentage of 93.3%. Research conducted by Hadi & Permatasari [12] showed that the diameter of the incision wound in rats was smaller and healed faster when given a topical mixture of cherry leaf and fruit extracts compared to topical cherry fruit or cherry leaf extract alone. This topical mix may be due to the combination of the two, which will increase the amount of bioactive content such as alkaloids, flavonoids, saponins, and tannins.

Flavonoids act as anti-inflammatory and antidiabetic, alkaloids and tannins act as antibacterial, and polyphenols act as antioxidants. The anti-inflammatory mechanism of flavonoids from cherry leaf extract through several pathways, namely inhibition of cyclooxygenation (COX) and lipoxygenation enzyme activities, inhibition of leukocyte accumulation, and inhibition of neutrophil degranulation. Inhibition of cyclooxygenation and lipoxygenation enzymes on inflammatory activity can inhibit the synthesis of leukotrienes and prostaglandins, mediators of inflammation. Inhibition of leukocyte accumulation occurs due to the inhibition of cyclooxygenation so that thromboxane will be inhibited. This process can cause a decrease in the body's response. The inhibition of neutrophil degranulation disrupts the release of arachidonic acid by neutrophils.

Saponins can interact with many membrane lipids, such as phospholipids, precursors of prostaglandins, and other inflammatory mediators [13]. The mechanism of alkaloids in the inflammatory process is by suppressing the release of histamine by mast cells and reducing the secretion of IL-1 by monocytes and PAF (platelet activating factors) on platelets [14].

Iron is an essential element in wound healing. Cherry leaves contain various phenolic compounds, one of which is polyphenols. Polyphenols have the potential to interfere

with iron absorption. However, if the polyphenol content is too much, it can inhibit the wound-healing process [15].

F. *Increase the number of macrophages*

The flavonoids in this cherry leaf extract ointment trigger the action of macrophages to phagocytose debris cells and microorganisms in the wound, thereby accelerating the inflammatory process. The saponin content in cherry leaves can also trigger the formation of VEGF and increase the number of macrophages that migrate to the wound area [8]. Previous research also showed that 20 per cent cherry leaf extract gel could improve the process of gingival wound healing in Wistar rats by increasing the number of macrophages three days after injury [16].

Cells that play a role in the body's defence system such as Macrophages, neutrophils, and monocytes, which play a role in the body's defence system, are very helpful in creating an infection-free wound-healing atmosphere where this condition is indispensable for wound healing [17]. One of the essential functions of macrophages is their ability to promote angiogenesis through the initiation of VEGF production. VEGF is a potential proangiogenic factor wherein several studies have shown VEGF has a 50% contribution to angiogenic activity in wounds. Other interpretations of previous studies also show that macrophages have a direct or indirect effect. For example, macrophages initiate the production of PDGF, which acts as a recruiter for progenitor cells and inflammatory cells [19].

G. *Reduces migration of polymorphonuclear cells (neutrophils, eosinophils, and basophils) on the fifth day*

The wound healing process consists of three phases, namely the inflammatory phase, the proliferative phase, and the maturation phase. The inflammatory phase is the body's initial reaction to protect foreign objects that enter the body. Cells that play a significant role in this phase are PMN cells in killing bacteria that cause infection. Neutrophils will first appear in the inflammatory area in the first 6 to 24 h and the highest on the third day. Neutrophils will begin to undergo apoptosis and be replaced by monocytes as macrophages. After the third day, the neutrophils will gradually decrease in number so that they disappear on the third day [14]. The results showed that cherry leaf extract ointment with a concentration of 40% and 50% significantly affected the migration of polymorphonuclear cells on the fifth day of administration. The assumption is that the higher the extract's concentration, the more active substances in cherry leaves that act as antibacterial [7].

Flavonoids in cherry leaves have an antibacterial effect. The mechanism of action of flavonoids can release transduced energy to the bacterial cytoplasmic membrane, inhibit bacterial motility, and then damage the permeability of the bacterial cell wall. The content of saponins works by disrupting the stability of bacterial cell membranes and causing bacterial cell lysis and the release of various essential components in bacterial cells, such as proteins, nucleic acids, and nucleotides [18].

H. *Increases collagen, epithelium, and new blood vessels (angiogenesis)*

The wound-healing process requires a lot of blood vessels to help accelerate healing by increasing oxygen circulation and tissue perfusion [21]. Giving cherry leaf extract

ointment with a concentration of 50% has a better ability to increase the angiogenesis process so that it can accelerate the healing process of hyperglycemic mice skin incisions [9]. Faster blood vessel growth due to the administration of cherry leaf extract in the form of an ointment containing flavonoids, saponins, and tannins which are known to have proangiogenic effects to support wound healing in terms of blood vessel formation (angiogenesis) and can also increase VEGF expression as a stimulator of angiogenesis [18]. Flavonoids contained in cherry leaves are useful as anti-inflammatory, antioxidant, and antimicrobial by increasing vascularization and reducing edema. Tannins are antimicrobial, increase epithelialization, and are thought to play a role in the regulation of VEGF transcription and translation.

Meanwhile, saponins are known to stimulate angiogenesis by stimulating and increasing VEGF production, accelerating the inflammatory phase, and accelerating the wound-healing process [20]. The method of angiogenesis that produces blood vessels plays a role in maintaining the continuity of the function of various affected tissues or organs, providing oxygen, nutrients, and inflammatory cells, and eliminating necrotic tissue. The more blood vessels are found, the faster the tissue repairs, so the wound-healing process is more immediate [22].

4 Research Limitations

Topics with research on the cherry leaf as a topical in diabetes are scarce, so references are very few because the cherry is a plant that lives in tropical countries.

5 Conclusion

Cherry leaf extract can accelerate wound healing in diabetic mice when an ointment or gel is made with preparations of 0%, 30%, 40%, and 50%. The benefits of cherry leaf extract in diabetic wound healing are by reducing signs of inflammation, scab, and wound diameter; increasing the number of macrophages; decreasing migration of polymorphonuclear cells (neutrophils, eosinophils, and basophils) on day five; and increasing collagen, epithelium and new blood vessels (angiogenesis).

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