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The Effectiveness of *Asiatic Acid, Asiaticoside*, and *Madecassocide* in *Centella Asiatica*, (Linn), Urb. on the Healing Process of Infected Wounds in Experimental Animals: Systematic Literature Review

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Abstract

A wound is a condition where body tissue is damaged as a result of sharp objects, chemicals, animal bites, electric shocks, and so on. Good and correct wound management can prevent wounds from becoming infected. In general, for infected wounds, aminoglycoside antibiotic ointments are used which are effective against gram-negative and gram-positive bacteria, such as gentamicin. Where the use of gentamicin ointment is still the "Drug of Choice" for infected wounds. However, due to several side effects that can be caused such as allergic reactions that will cause discomfort in patients with hypersensitivity to antibiotics in this group and the possibility of resistance to the use of this type of antibiotic, other alternative therapies have emerged for treating wounds with ingredients that have minimal side effects, one of which is by using traditional medicine from nature. One of the herbal medicines that is believed to be able to treat skin wounds is the Gotu Kola plant or *Centella asiatica*. The gotu kola plant or *Centella asiatica* contains several active substances that are useful in accelerating wound healing, namely *Asiatic acid, Madecassocide,* and *Asiaticoside*. This study aims to determine and assess the activity of these substances in *Centella asiatica* which play a role in the healing process of infected wounds in experimental animals. This research is a review article, by searching data from Google Scholar, PubMed, and NCBI databases with keywords used such as, "Effectiveness of Centella, Active Ingredients of Centella, Centella on Wounds". Many articles appear, but those used in this article that fit the inclusion criteria are 6 articles. The results of the 6 articles stated that *Centella asiatica* has the potential to heal infected wounds because it contains triterpenoid compounds which have antibacterial activity against *Staphylococcus aureus* and *Escherichia colli*. This review article concludes that the active substances found in pegagan leaves, namely *Asiatic acid, Madecassocide*, and *Asiaticoside*, have benefits in healing infected wounds in experimental animals.

Keywords: Effectiveness, Centella, Wounds

1. Introduction

Wounds are a condition where there is body tissue that is damaged due to sharp objects, chemicals, animal bites, electric shocks, and so on.[1] Skin wounds are often considered minor by everyone. In fact, wounds on the skin, especially open wounds that are not treated properly, can become contaminated wounds or infected wounds. For this reason, proper and correct wound care is an important thing that should not be underestimated because it can prevent wounds from various risks of infection so that wound healing becomes difficult.

Wound healing is a natural physiological reaction that occurs in tissue injury. For small wounds, wounds can usually heal on their own if the wound is not dirty and the wound is not infected. 4 phases occur in the wound healing process, namely the hemostasis phase, the inflammation phase, the proliferation phase, and the remodeling phase.[2]

1. **Hemostasis Phase** is a phase of the blood clotting process as a form of the

body's reaction to stop the bleeding that is occurring. This phase lasts for several minutes to hours immediately after the wound occurs.

2. **The inflammation Phase** is a form of physiological inflammation where in this phase there is a process of destroying all debris and preventing bacterial colonization by the immune system. This phase occurs within 1-5 days.
3. **Proliferation Phase**. There are 3 main processes that occur in this phase, namely neoangiogenesis, collagen formation, and re-epithelialization. This phase is marked by the proliferation of keratinocyte cells. This phase occurs from day 6-21 from the time the wound occurs.
4. **Remodeling Phase**. This is the final phase to maximize the structure of new tissue as a wound filler. This phase has started to occur in the second week or day 21 to 1 year.[2]

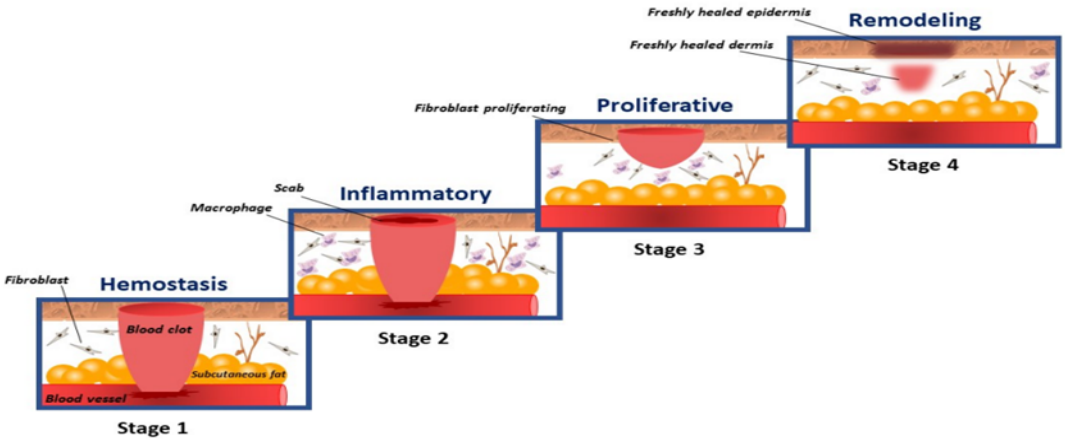

Figure 1. **Wound Healing Phases**[3]

Normally the healing time for wounds is around 14-21 days (Figure 1), but if the wound becomes infected, the healing time will be longer than usual, which is around 17-53 days.[4]

According to WHO data in 2012, the prevalence of infected wounds in Indonesia is around 2.3% - 18.3%.[5] Several factors can cause wounds to be slow to heal, with the main factor being infection in the wound.[6] For this reason, proper wound care is essential. In general, for infected wounds, aminoglycoside antibiotic ointments are used which are effective against gram-negative and gram-positive bacteria, such as gentamicin. Where the use of gentamicin ointment is still the "Drug of Choice" for infected wounds.[7] However, due to several side effects that can be caused such as allergic reactions that will cause discomfort in patients with hypersensitivity to antibiotics in this group and the possibility of resistance to the use of this type of antibiotic, other alternative therapies have emerged for treating wounds with ingredients that have minimal side effects, one of which is by using traditional medicine from nature. One of the plants in Indonesia that has the potential as a medicine for healing wounds and is easy to find is the Pegagan Plant or Centella Asiatica.

The pegagan plant or Centella Asiatica better known by the Indonesian people as the horseshoe plant is a type of wild plant that grows a lot in plantations, roadsides, and rice fields (Figure 4). It is called the horseshoe plant because the shape of the leaves of this plant resembles a horse's foot or hoof so people often call it the horseshoe plant. This

plant is not difficult to find in Indonesia. This plant has many health benefits. Since ancient times, this plant has been trusted by our ancestors in treating various diseases, namely wound medicine, keloids, ulcers, fever, asthma, high blood pressure, nervous disorders, and improving blood circulation. Several studies have stated that this plant has a good effect on wound healing because it has antibacterial and antioxidant activity. This plant has several contents that are beneficial for health such as triterpenoids, saponins, and tannins. The triterpenoids consist of asiatic acid, madecassocide, and asiaticoside. Asiatic acid has benefits as an antioxidant and anti-inflammatory. Madecassocide has benefits as an antioxidant and increases collagen synthesis. And Asiaticoside has benefits in increasing fibroblast proliferation, collagen synthesis, and neoangiogenesis. In addition, other benefits of Asiaticoside are as an antibacterial against Staphylococcus aureus and Escherichia colli. Where these three substances play a role in accelerating the wound healing process.[2,8]

The tannin content acts as an antioxidant, antimicrobial, and has a vasoconstriction effect on blood vessels and the creation of mechanical blockages to stop mild bleeding.[9] The saponin content itself acts as a strong surfactant like soap because it can increase membrane permeability. So that the essential ingredients needed by bacteria to live are lost and can cause death in bacterial cells.[1] For this reason, extracts from this plant can be used in healing infected wounds because they have antibacterial activity.

The purpose of this review article is to determine the effectiveness of these substances on the healing process of infected wounds in experimental animals.

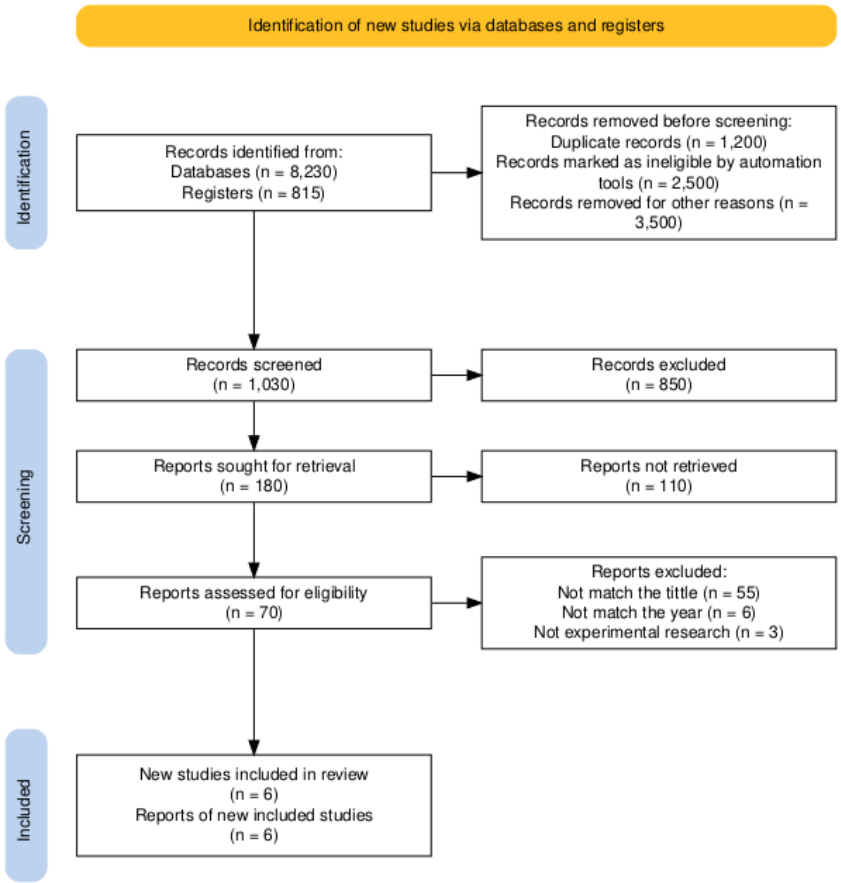

Figure 2. Prism Diagram

2. Methods

The method used in this article is Systematic Literature Review (SLR). Data search using Google Scholar, PubMed, and NCBI databases with the keywords used "Effectiveness of Centella, Active Substances of Centella, Centella in Wounds". Data screening was used based on inclusion criteria (full-text articles and experimental research in 2010 - 2023) and exclusion criteria, namely articles that do not discuss the active substances in Centella Asiatica, articles that do not discuss the benefits of Centella Asiatica for wound healing, and articles that cannot be fully accessed. Data quality assessment is selected based on PICOS criteria. Population: experimental animals, Intervention: administration of Centella Asiatica, Comparison: no treatment or administration of drugs other than Centella Asiatica extract to animals being tested and compared with experimental animals given positive controls, Outcome: healing process. Study: true experimental research. The data used are in the form of research articles published in national and international journals. The results of the articles obtained will be analyzed.

3. Results

The search results on the databases, namely Google Scholar, Pubmed, and NCBI, found 6 articles that met the inclusion and exclusion criteria based on the assessment with the PICOS criteria. So these 6 articles meet the requirements for analysis (Figure 2). The results of the review of the effectiveness of asiatic acid, madecassocide, and asiaticoside on healing infected wounds in experimental animals can be seen in table 1.

Based on the results of the experimental study above, the content of compounds in Centella asiatica can accelerate the wound healing process. This is due to the presence of active compounds such as Asiatic acid, Asiaticoside, and Madecassocide which play an important role in each phase of wound healing. Giving Centella asiatica extract with a concentration of 25% for contaminated wounds gave the best effect compared to concentrations of 50% and 75% as shown in Table 1. In rat incision wounds, giving gotu kola leaf extract ointment did not have a significant effect on wound healing. Giving gotu kola leaf extract to rat incision wounds showed the same effect as giving gentamicin ointment.

Giving gotu kola leaf extract to rat incision wounds affected accelerating wound healing compared to rats that were not given anything or those given 10% iodine. The formulation of gotu kola leaf extract ointment with an oil base or pure extract was more effective in healing wounds compared to giving extract ointment with an emulsion base and a water-soluble base on the 14th day. However, on the 21st day, all groups were effective in healing wounds. Administration of gotu kola leaf extract gel has also been shown to increase neovascularization, the number of fibroblasts in mice, and epithelialization in healing mouse wounds as shown in Table 1.

4. Discussion

Wounds are one condition that cannot be underestimated. All types of wounds can potentially become infected wounds if the wound is dirty and does not receive the right and adequate regimen or therapy. There are stages at which a wound can become infected, namely contamination, colonization, and infection. Contamination can be described if there is an open wound, and there are microbes in the wound but the microbes cannot replicate so the number is minimal, therefore the number of microbes cannot affect the normal inflammatory immune response and the wound healing process.

Then to the colonization stage, if the microbes in the open wound have replicated but have not been able to cause infection in the wound. The next stage is infection where the microbes have replicated rapidly, and the microbes have migrated to the base of the wound so that they can trigger local and systemic immune reactions (Figure 3).

Table 1. **Conclusion of Review Articles that are in accordance with the Effectiveness of Asiatic Acid, Madecassocide, and Asiaticoside on Healing Infected Wounds in Experimental Animals**

Title	Writer	Parameter	Results
Effect of Centella Asiatica Leaf Extract in Accelerating Healing of Contaminated Wounds in White Rats (*Rattus Novergicus*) Wistar Strain	Sholihatul Amaliya, Bambang Soemantri, Yulian Wiji Utami. 2013	Macroscopically, there are several indicators of signs of wound healing, namely the disappearance of erythema, the disappearance of edema, the disappearance of pus, and the edges of the wound closing.	Gotu kola leaf extract can accelerate the healing of contaminated wounds.[10]
Effect of Giving *Centella Asiatica* Leaves Extract Ointment On Wound Healing of Male White Rats (*Rattus Norvegicus*)	Debby E. Galomat, Edwin de Queljoe, Olivie S. Datu. 2021	Macroscopically, by measuring the length of the wound & swelling of the wound using a vernier caliper	The results of statistical analysis showed that there was no significant difference between each treatment group with different concentrations of pegagan extract ointment.[1]
Comparison of the Effectiveness of Pegagan Extract (*Centella Asiatica*) with Gentamicin Ointment on Healing of Incision Wounds in Sprague Dawley White Rats	Helena Vaustina Anu, Anita Lidesna Shinta Amat, I Nyoman Sasputra. 2019	Macroscopically, using the Nagaoka criteria.	The macroscopic effect of healing incision wounds by administering pegagan leaf extract and gentamicin provided the same wound-healing effect.[11]
The Effect of Giving Pegagan Leaf Extract (Centella Asiatica) on Healing of Cut Wounds in Male White Rats (*Rattus Norvegicus*) Wistar Strain	I Made Subhawa Harsa. 2020	Macroscopically, the criteria for wound healing using the scoring system, namely dry skin conditions, wound color, no signs of infection (pus/exudate), no necrotic tissue, no erythema, and no edema.	Administration of pegagan leaf extract to heal cut wounds in mice has been shown to accelerate wound healing compared to positive controls (10% iodine) and negative controls (nothing given).[12]
Effectiveness of Pegagan Herb Extract Ointment Preparation (*Centella Asiatica* (L) Urb) for Wound Healing in Male Mice (*Mus musculus albinus*)	Moerfiah, Muztabadihardja, Santi Puspita Dewi. 2014	Macroscopically, by observing the wound healing process such as skin tightening, wound drying, and the presence of wound scabs.	Pegagan herb extract ointment is effective in healing wounds in male mice and the oily ointment base is more effective in healing wounds compared to the emulsion base and water-soluble base.[8]
The Effect of Giving Pegagan Leaf Extract Gel (*Centella Asiatica*) as an Enhancer of Neovascularization, Fibroblasts, and Epithelialization in Wound Healing in Male Rats	Gempita Cahaya Aulia Tambunan, Erni Girsang, Ali Napiah Nasution. 2023	Histopathological examination by assessing the amount of neovascularization, thickness of epithelialization, and number of fibroblasts.	Administration of pegagan leaf extract gel in the results increased neovascularization, epithelialization, and the number of fibroblasts in male rats. Concentrations of 1000 mg/kg of both extracts provided hepatoprotective,

antioxidant, and antiapoptotic effects.[9]

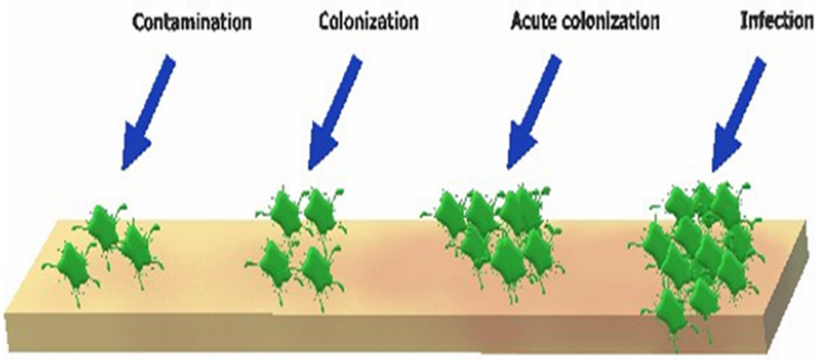

Figure 3. Stages of Wound Infection[13]

Table 2. Factors Affecting Wound Healing[14]

Factors Influencing The Wound Healing	
Local Factors	**Systemic Factors**
Oxygenation	Age, gender
Foreign Body	Disease: diabetes, keloids, fibrosis, uremia, jaundice
Blood Supply	Medications: NSAIDs, chemotherapy, glucocorticoid
	Stress, alcohol, nutrition
	Immunocompromised status, cancer, AIDS, radiation

NSAIDs: Nonsteroid anti-inflammatory medications
AIDS: Acquired immune deficiency syndrome

Figure 4. Gotu Kola Plant[17]

Several factors can cause wounds to be slower to heal than they should (Table 2). The main factor that affects the duration of wound healing is infection.[6] Therefore, proper and adequate wound care is very important so that the wound does not cause deeper tissue damage. Based on the onset or length of time needed for wound healing, wounds are divided into 2, namely acute wounds and chronic wounds.[15] Acute wounds heal according to the length of time for normal wound healing or according to predictions (Figure 1), while chronic wounds take longer due to several factors that accompany the wound so that the wound becomes difficult to heal as shown in Table 2.

Triterpenoids are one of the most dominant active substances contained in the pegagan plant or Centella asiatica, (Linn), Urb. Triterpenoids consist of Asiatic acid, Asiaticoside, and Madecassocide which play a role in the wound healing process as shown in Table 3. Asiatic acid pharmacologically functions as an antioxidant, anti-inflammatory, and plays a role in controlling cell apoptosis which in various diseases has an impact on treatment. In addition, Asiatic acid also has effects as an antihypertensive, neuroprotective, antidiabetic, antimicrobial, and antitumor which are quite strong. This is because this compound can affect the work of several enzymes, growth factors, receptors, cell apoptosis, and cell signaling.[16] Madecassocide functions as an antioxidant and also increases collagen synthesis. Asiaticoside itself also functions in collagen

synthesis, fibroblast proliferation, angiogenesis (growth of new blood vessels), and as an antibacterial against *Staphylococcus aureus* and *Escherichia colli.*[2,8]

Table 3. Types of Phytochemicals and Their Functions[17]

Types of Phytochemicals	Function	Group	Reference
Alkaloid	As a medicine, a poison, a detoxification of metabolic products, a growth regulator, and a provider of nitrogen elements needed by plants.	Piridin, tropen, kinolin, isokinolin, indol, imidazol, purin, amin, and steroid.	Mursyidi (1990)[18]
Saponin	• Toxicity in cold-blooded animals causes irritation that causes vomiting and diarrhea. • As a bactericide, fungicide, amoebicide, and insect control • For anesthetics, sedatives, and anxiety relievers (antianxiety) • Madecassoside can stimulate collagen production which plays a role in the regeneration of skin cells, including egg cells (ovum) in women and sperm cells in men	Brahmosida, brahminosida, and madecassocide	Vickery and vickery (1981)[19] Puspa dkk (2023)[20] Irma dkk (2017)[21]
Flavonoid	• Ultraviolet light filter • Protects cells from ultraviolet B radiation (280 - 320 nm) • Protects leaf tissue damage	Kaemferol, kuersetin, glikosida (3-glukosilkuersetin and 3-glukosilkaemferol), Flavonoid O-glikosida and C-glikosida	Vickery and Vickery (1981)[19] Taiz and Zeiger (2002)[22] Musyarofah *et al*. (2007)[23] (Wren 1956)
Steroid	Microorganism energy and hormone activity in animals Estrogen and stigmasterol as vitamins or anti stiffness factors	Tetrasiklik triterpenoid, kampesterol, sitosterol, and stigmasterol	Vickery and Vickery (1981)[19]
Triterpenoid	• Antileprosy and antileprosy • Stimulates the formation of fats and proteins important for skin health • Converts proline and alanine into collagen for skin care • Accelerates healing of post-operative wounds, acne, and dark spots on the skin.	Asiaticoside, Asiatic Acid, Madecassocide	Dalimartha (2000)[24]

5. Conclusion

Research findings presented in this study indicate that the active compounds in Centella asiatica, specifically triterpenoids such as Asiatic acid, Asiaticoside, and Madecassocide, have demonstrated efficacy in expediting the healing of infected wounds in experimental animals due to their antimicrobial properties against Staphylococcus aureus and Escherichia coli. The microorganism most frequently responsible for causing inflammation or infection of the skin is Staphylococcus aureus, as it resides within the normal flora of the epidermis.

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