



**BENEFITS OF GOTU KOLA LEAF IN RESPONDING TO PREVENT THE FORM OF KELOID IN THE WOUND**

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**ABSTRACT**

Keloids are a type of scar, which is the result of overgrowth of dense fibrous tissue that usually develops after healing a skin injury. Keloids occur due to prolonged inflammatory phases in the wound, resulting in increased fibroblast activity and continuous extracellular matrix formation. Gotu kola (*Centella asiatica*) leaves are effective in the treatment of wounds because they contain Triterpene components such as asiatic acid, madecassic acid, asiaticoside and madecassoside. The purpose of this literature review is to report the latest scientific findings on the role of gotu kola leaf content in preventing keloid formation by increasing fibroblast proliferation, increasing collagen synthesis and mucopolysaccharide acids, increasing intracellular fibronectin which then significantly increases the tensile strength of newly formed skin, inhibiting the phases of the formation of skin, inflammation of the keloid scar tissue. The method used in this article is article search through the NCBI database and Google Scholar. The year of publication of library resources is from 1999 to 2018 with 20 sources of literature. The theme collected was related to the *Centella asiatica* leaf content towards the wound phase to prevent keloid formation. The results of the synthesis of articles that have been found are gotu kola leaves can inhibit the formation of keloids in wounds.

**Keywords:** gotu kola leaf, keloid, wound

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**INTRODUCTION**

Keloid is a type of scar, which results from overgrowth of dense fibrous tissue which usually develops after healing a skin injury. The tissue extends beyond the original wound boundary, usually does not undergo spontaneous regression and tends to recur after excision. Keloid is lesion with characteristically hard, springy, shiny fibrous nodules that vary from pink or red to dark brown. Keloid scars are benign, not contagious, and sometimes accompanied by intense itching or pain and can affect the movement of the skin (Alster & Tanzi, 2003). Keloids are characterized by over deposition of the extracellular matrix, namely collagen, fibronectin, elastin, proteoglycans, and growth factors such as TGF- $\beta$  (Halim *et al.*, 2012).

Keloid can occur in all parts of the body but are more common in the shoulders, chest, neck, upper arms and cheeks (Kakar *et al.*, 2006). Risk factors for keloid formation in scars

include family history of keloids, genes that are thought to have a role for keloids, namely HLA-B14, HLA-B21, HLA-BW16, HLABW35, HLA-DR5, and HLA-DQW3. In blacks, the risk of developing keloids increases up to 15 times greater. Another factor is hormones, during puberty and pregnancy the incidence of keloid increases and decreases during menopause (Sinto, 2018). In Indonesia, based on observational research conducted at Dr. Soetomo Hospital Surabaya, in 30 cases of keloids, data obtained that 76.7% of the most keloid sufferers were women at the age of 10-30 years (Andisi *et al.*, 2016)

Keloids occur due to prolonged inflammatory phases in the wound, resulting in increased fibroblast activity and continuous extracellular matrix formation. Transform Growth Factor beta also has a role in keloid formation, TGF- $\beta$ 1 and TGF- $\beta$ 2 are stimulants in collagen and proteoglycan synthesis and affect extracellular matrix which not only enhances collagen synthesis but also inhibits its breakdown resulting in the formation of scar tissue. (Sinto, 2018). In keloid scarring, surgery as a treatment effort often causes keloids to become larger due to surgical wounds. For this reason it is important to prevent the formation of keloids with therapy in the early stages of the wound.

Gotu kola (*Centella asiatica*) leaves are effective in the treatment of wounds, namely infected wounds, burns, hypertrophic scars or postoperative keloids. The components that play a role in wound healing are Triterpene components such as asiatic acid, madecassic acid, asiaticoside and madecassoside. Terpenoids cause a significant increase in the percentage of collagen and fibronectin cell layers. The most beneficial effects are the stimulation of scarring maturation by the production of type I collagen, decreased inflammatory reaction and myofibroblast production (Widgerow *et al.*, 2000). Asiaticoside also stimulates angiogenesis so that increased tension and elasticity of blood vessels are observed. The mechanism of action of asiaticoside is the induction of type I collagen synthesis in skin fibroblast cells by activating the Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) receptor I kinase (Lee *et al.*, 2006). The active madecassoside content also has a role in wound healing, through increased antioxidant activity and increasing collagen synthesis, as well as influencing angiogenesis (Liu *et al.*, 2008).

## **METHOD**

The method used in writing this article is literature review. Literature sources used in this article involve 20 libraries both from books, national or international journals, and websites. Literature search in this article through NCBI and Google Scholar databases with keywords Keloid, Scar, Wound, Centella asiatica. The selection of literature sources is done by reviewing the title and abstract, which discusses the influence of gotu kola leaf content on the wound phase to prevent keloid formation. The year of publication of library resources in writing this article is 1999 to 2018.

## **RESULTS**

Gotu kola leaf ethanol extract increased the synthesis of collagen threefold from human fibroblast cells compared with grape seed extract and vitamin C. The highest collagen synthesis was found at 50 mg/mL of gotu kola leaf extract. This extract showed significant DPPH radical uptake activity with 84% inhibition at a concentration of 1 mg/mL (Hashim

*et al.*, 2011). Effect of asiaticoside content in gotu kola leaves on normal human skin cells, studied by Lee *et al.* In vitro studies prove that asiaticoside affects the proliferation of fibroblasts in the skin also increases migration and accelerates the attachment of skin cells so that there is no prolongation of the inflammatory phase which causes scarring of hypertrophy and keloids (Lee *et al.*, 2012).

Ethanol extract from gotu kola leaves plays a role in wound healing in normal wounds and in wounds that are suppressed by dexamethasone. The study was conducted on Wistar albino rats using incision, excision, and dead space incision models. The results obtained by histological observation that gotu kola leaf extract has an effect similar to wound healing by using dexamethasone on all wound models (Shetty *et al.*, 2006).

Gotu Kola leaf extract can shorten the wound healing process in diabetic patients. Randomized control study conducted on 200 diabetic patients, treated with two capsules of *C. asiatica* extract (50 mg asiaticoside/capsule) three times a day. Results showed better wound contraction in the group given gotu kola leaf extract compared with the placebo group. In addition, gotu kola leaf extract can suppress the formation of scar tissue such as keloids (Paocharoen, 2010).

## **DISCUSSION**

In general, scar or scar tissue is divided into two namely hypertrophic scar tissue and keloid. Hypertrophic scarring is usually preceded by trauma and the extent of scarring does not exceed the area of the wound. Keloids can be preceded by trauma and sometimes can occur spontaneously without injury. Scar tissue in the keloid can be wider than the area of the wound. (Maghrabi & Kabel, 2014).

Pathophysiologically, wound healing is divided into three main stages (Sinto, 2018), those are: (1)Inflamation phase: it starts when a wound occurs and lasts up to three days. The process begins with vasoconstriction to achieve homeostasis. Blood releases growth factors such as Platelet Derived Growth Factor (PDGF) and Transforming Growth Factor beta (TGF- $\beta$ ). Neutrophils reach the wound area and fill the wound cavity. Neutrophils will phagocyte dead tissue and prevent infection. Furthermore, the monocytes will enter the wound area. Macrophages phagocyte debris and bacteria and play a role in the production of growth factors needed for the manufacture of extracellular matrix by fibroblasts and new blood vessels for wound healing. (2)Proliferation phase: this phase starts on the 4th day until the 3rd week after the wound. Macrophages continue to produce growth factors such as PDGF and TNF- $\beta$ 1 that make fibroblasts continue to proliferate and migrate to form extracellular matrix networks. In addition, it also stimulates endothelial cells to form new blood vessels. Type III collagen also begins to form which will be replaced by type I collagen in the remodeling phase. (3)Remodelling phase: the longest phase in the wound healing phase, lasts from the 3rd week to 1 year. This phase is characterized by wound contractions and collagen remodeling. Type I collagen begins to replace type III collagen. The strength of the wound continues to increase with the reorganization of collagen.

The elongated inflammatory phase is one of the causes of hypertrophic scarring or keloids. The increasing number of immune cells in keloids increases fibroblast activity and the formation of extracellular matrix continues. This is also thought to cause keloids, scar tissue arising beyond the wound limit. Transforming Growth Factor- $\beta$  or TGF- $\beta$  also has a role in the occurrence of these fibrotic tissue abnormalities. TGF- $\beta$ 1 and TGF- $\beta$ 2 are stimulants in collagen and proteoglycan synthesis and affect extracellular matrix which not only increases collagen synthesis but also inhibits its breakdown. Whereas TGF- $\beta$ 3 which is found to be more dominant in the final phase of wound healing has the opposite function. Decorin is a proteoglycan which has the ability to bind and neutralize TGF- $\beta$  and decrease extracellular matrix proteins. Low decorin levels can trigger fibrotic abnormalities (Sinto, 2018).

Based on an understanding of the pathogenesis of keloids currently available, there are three therapeutic approaches that can be used, namely manipulation of the mechanical aspects of wound healing, correction of the imbalance between collagen synthesis and degradation, and changes in response/inflammation (Lester & Thompson, 1999). Management of keloids is a difficult problem, because of the low healing response to various therapies and tends to recur. Keloids that are only treated surgically have a recurrence rate of up to 80% (Berman *et al.*, 2005). For this reason it is important to prevent the formation of keloids with therapy in the early stages of the wound.

Gotu kola leaf or *Centella asiatica* (L.) synonym of *Hydrocotyle asiatica* L. also known by the common name as: Gotu kola or Tiger Grass, included in the Apiaceae family. Grows in Asia, especially in India, Pakistan, Madagascar, equatorial Africa, central America and in the tropical regions of Oceania (Brinkhaus *et al.*, 2000). Gotu kola leaf is an important medicinal herb that is widely used in the Eastern world and is becoming popular in the West. Triterpenoids, saponins, the main constituents of *Centella asiatica* are believed to be male responsible for their extensive therapeutic actions. In addition to wound healing, this herb is recommended for the treatment of various skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis, diarrhea, fever, amenorrhea, diseases of the female genitourinary tract and also to eliminate anxiety and improve cognition (Gohil *et al.*, 2010).

Pharmacological studies include *Centella asiatica* (TECA) titration extract, total triterpenoid fraction from *Centella asiatica* (TTFCA), both containing asiatic acid (30%), madecassic acid (30%), asiaticosides (40%) and total triterpenic fraction (TTFCA), both containing asiatic acid (30%), madecassic acid (30%), asiaticosides (40%) (Brinkhaus *et al.*, 2000). The effect of asiaticoside on collagen synthesis and proliferation of keloid-derived fibroblasts was also investigated by Tang *et al.* Keloid scars occur as a result of pathological wound healing, characterized by hyperproliferation of keloid fibroblasts, overproduction of extracellular matrix, deviant cytokines and growth factor activity. The TGF- $\beta$  pathway, especially TGF- $\beta$ 1, is involved in keloid formation. Prolonged healing of the wound can cause an imbalance in TGF- $\beta$ 1 expression and thus can cause fibroproliferative disorders and excessive scar formation (Tang *et al.*, 2011) Asiaticoside inhibits TGF- $\beta$  receptor protein and mRNA expression, increases Smad-7 protein and mRNA expression, whereas it does not change Smad-2, Smad-3, Smad-4, expression and

Smad-2 phosphorylated and Smad-3 (reduction of TGF expression - $\beta$ R1 leads to decreased expression of R-Smads) in keloid scars. Asiaticoside has a dual role by promoting wound healing and preventing scar formation (Bylka *et al.*, 2014).

## CONCLUSION

Keloids are a type of scar, which results from overgrowth of dense fibrous tissue which usually develops after healing a skin injury. The formation of keloids can be inhibited by using gotu kola (*Centella asiatica*) which has triterpene components such as asiatic acid, madecassic acid, asiaticoside and madecassoside. Its mechanism of action is to increase fibroblast proliferation, increase collagen synthesis and mucopolysaccharide acid, increase intracellular fibronectin and mitotic activity in the germ lining, which then significantly increases the tensile strength of newly formed skin, and inhibit the inflammatory phase of hypertrophic and keloid scarring. So, Gotu kola leaf (*Centella asiatica*) can be used as an alternative to preventing the formation of keloid scarring in wounds.

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