



A Systematic Review of Randomized Controlled Trial on Efficacy of *Centella asiatica* for Wound Healing

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Received June 30th, 2022

Accepted July 12th, 2022

Published July 21st, 2022

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ABSTRACT

Introduction: The delay of wound healing leads to the risk of infection, chronic wound and other complications. Proper treatments for wound care will speed up the healing process and reduce scar formation. *Centella asiatica* is the famous medicinal plant among herbal skin care for healing both normal and chronic wounds with less adverse effects.

Objective: This systematic review was performed to evaluate the wound healing properties of *C. asiatica* in clinical trials.

Methods: A pre-registered systematic review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy and three electronic databases including PubMed, ScienceDirect and Google Scholar were used in this study. We had intended to perform a meta-analysis, but this was not possible due to variation in study design and reporting. The search strategy identified 1,410 articles through selected databases and 5 clinical trials met the inclusion criteria for quantitative synthesis. The quality assessment for risk of bias of the selected studies was evaluated by Cochrane risk of bias tool. The inclusion criteria were randomized controlled trials. We included participants with wounds regardless of age, gender, and ethnicity. The different types of wound are burn wound, diabetic foot ulcer, hypertrophic scar, split-thickness skin graft, and post laser resurfacing.

Results: The favorable effect of *C. asiatica* was observed with a quicker wound healing, possibly due to the synthesis of collagen type 1, 2, and 3, stimulation of fibronectin, and remodeling of the extracellular matrix. Furthermore, *C. asiatica* has a beneficial effect on anti-inflammation and increases tensile strength, accelerating the formation of epithelium and keratin.

Conclusion: *C. asiatica* may have beneficial effects on wound healing; however, more clinical trials are needed in order to perform a meta-analysis to ensure the wound healing effects of the plant in different parameters.

Keywords: *Centella asiatica*; wound healing; clinical application

Introduction

Centella asiatica is a tropical herbaceous perennial plant in the Apiaceae family. The plant can be found abundantly in many tropical and subtropical countries worldwide such as Thailand, China, India and Sri Lanka [1]. *C. asiatica* is a common culinary vegetable with high nutrition and it has been traditionally used as a

medicinal herb to treat skin problems as well as to heal wounds [2]. In Thai traditional medicine, the plant is called Bao-Bok which has a cold property with a bitter taste, thus it is recommended to treat the diseases with hot symptoms e.g. inflammation. Additionally, the whole plant has been used to dispel heat, accelerate wound healing, reduce keloid formation, treat burns,

bruises, mouth ulcers as well as relieve heartburn and thirst [3]. Many studies reported that *C. asiatica* have positively promoted wound healing by improving collagen synthesis [4, 5] and microcirculatory function [6, 7]. However, most of the studies have been done in animal and in vitro models.

Wound healing is a natural process occurred in human body. There are four main phases of cellular and bio-physiological events for normal wound healing steps including hemostasis, inflammation, proliferation and remodeling [8]. In addition, there are two main factors that can delay wound healing, including: factors local to the wound itself (desiccation, infection or abnormal bacterial presence, maceration, necrosis, pressure, trauma, and edema) and systemic factors (age, body type, chronic disease, immunosuppression, nutritional status, radiation therapy, and vascular insufficiencies) [9]. The aforementioned factors impaired the healing process of wound which can lead to the pathologic inflammation of the wounds [10].

Numerous studies of *C. Asiatica* were investigated with various types of wounds and scar such as burns [11], diabetic foot ulcer [12], laser resurfacing wounds [13], split-thickness skin graft wounds [14], acne scars [15] hypertrophic scars and keloids [16].

From the aforementioned studies, there are various types of wounds treated with *C. asiatica* in clinical trial settings. All of them revealed the effectiveness of *C. asiatica* as the treatment for various kinds of wounds; however, the data have been heterogeneous on the outcome and in which type of wounds this plant should be employed. This systematic review evaluated the current evidence on *C. asiatica* in clinical trial settings (randomized controlled trial) for wound healing which is needed to provide an evidence base for researchers and practitioners. The evidence is assessed to guide clinical decision making and to further facilitate future research in a timely manner.

Methodology

This systematic review was reported according to the 2015 PRISMA recommendation [17]. The protocol of this study was previously registered with the Prospero registration no. CRD42021284821.

Search strategy

The literature search was performed by 3 authors, searching the following electronic bibliographic English databases: PubMed, ScienceDirect, Google Scholar. All databases were searched from the available date of inception through 4 September 2021. The following keywords were used: centella AND wound AND random AND clinic, centella AND wound healing AND random AND clinic, Centella asiatica AND wound AND random AND clinic, Centella asiatica AND wound healing AND random AND clinic, Gotu kola

AND wound AND clinical AND random, Gotu kola AND wound healing AND clinical AND random. Three authors independently screened the titles and abstracts for eligibility. All searches were re-conducted before the completion of this review, to retrieve any further includable studies.

Selection process

Inclusion criteria: the studies were eligible if they were randomized controlled trials (RCTs) that included *C. asiatica* for wound healing. We included participants with wounds regardless of age, gender, and ethnicity. The different types of wounds are: burn wound, diabetic foot ulcer, hypertrophic scar, split-thickness skin graft (STSG), acne and post laser resurfacing. Exclusion criteria: the studies were those not conducted on humans; those not including supplementation or topical treatment with *C. asiatica* or any of its extracts; and those involving participants under 18 years of age. The reason for excluding studies with participants younger than 18 years is due to the metabolic stress that is present during growth. Studies in another language other than English were also excluded from the review. No publication date restrictions were applied (Figure 1).

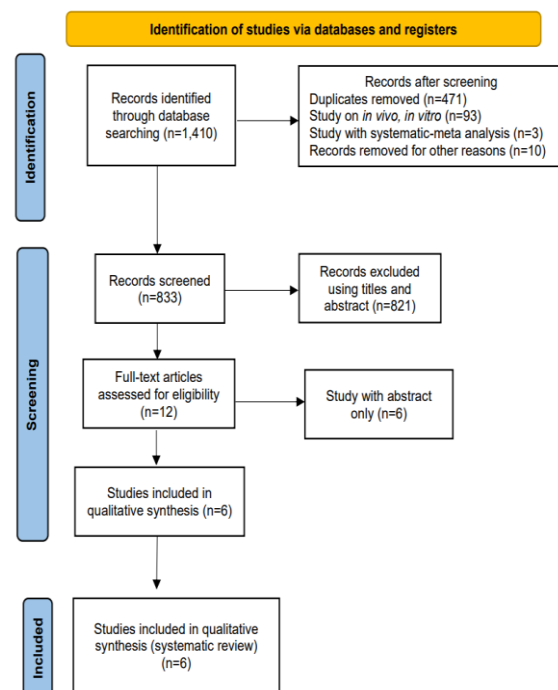


Figure 1. Flow diagram of the search strategy

Intervention groups

Use a topical ointment containing *C. asiatica* or herbal extracts containing mainly *C. asiatica* were included with the duration of treatment for at least 2 weeks.

Comparison groups

Comparison groups that received placebo or only western medications treatment were included.

Outcomes

The outcomes included in the review were: Wagner grade, skin erythema, re-epithelialization, VSS (vascularity, pigmentation, pliability, height), and VAS (visual acuity score).

Quality assessment

Three reviewers individually assessed the risk of bias of the included studies by the Cochrane risk of bias

tool (The Cochrane Collaboration, Copenhagen, Denmark) [18]. There are seven domains for evaluation including random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Three symbols including a plus (+), a question mark (?) and a minus (-) were used to indicate low risk of bias, unclear risk of bias, and high risk of bias, respectively.

Results

Five clinical randomized controlled trials [14, 15, 19-21] on wound healing utilizing *C. asiatica* were included in the current systematic review (Table 1).

Table 1 Summary of included studies

Author (Year)	Sample Size (Male/Female)	Duration	Model	Intervention	Control	Results
Yuan-Sung Kuo et al. (2012)	WH-1 cream: (4/8) hydrocolloid group: (5/7)	2 weeks	Diabetic foot ulcer	WH-1 cream containing <i>P. amboinicus</i> and <i>C. asiatica</i> in a 1: 4 ratios	Hydrocolloid fiber dressings	☑ Wagner grade improvement, ☑ Reduction in wound size (postsurgical debridement)
Amin Saeidinia et al. (2017)	CA group: (9/21) SSD Group: (10/20)	2 weeks	Burn wound	Centiderm ointment (CA)	1% Silver sulfadiazine cream (SSD)	☑ Vancouver Scar Scale (VSS) score, ☑ Visual acuity score (VAS) score, ☑ Re-epithelialization, ☑ Healing time, ☑ Infection, ☑ Pigmentation
Kamonwan Jenwitheesuk et al. (2018)	N = 23	12 weeks	split-thickness skin graft (STSG)	7% w/w Centella asiatica extract in cream preparation	Placebo	☑ Vancouver Scar Scale (VSS) score ☑ Pigmentation
Palakorn Surakunprapha et al. (2020)	Herbal extract + silicone gel: (10/14) Placebo gel: (14/10)	6 months	Hypertrophic scar	15% Herbal extract mixture (<i>Allium Cepa</i> extract, <i>Centella Asiatica</i> extract, <i>Aloe Vera</i> extract and Paper Mulberry extract) + silicone gel	Placebo	☑ Scar amelioration in height ☑ pliability ☑ vascularity ☑ pigmentation
Wilawan Damkerngsunto et al. (2020)	0.05% w/w Eca 233 gel: (5/25) Placebo gel: (5/25)	3 months	Post laser resurfacing	0.05% w/w ECa 233 gels	Placebo	☑ Erythema, ☑ Wound appearance, ☑ Epithelialization

Risk of bias assessment

Risk of bias among five articles was summarized in figure 2. The articles in the studies were categorized as low risk of bias.

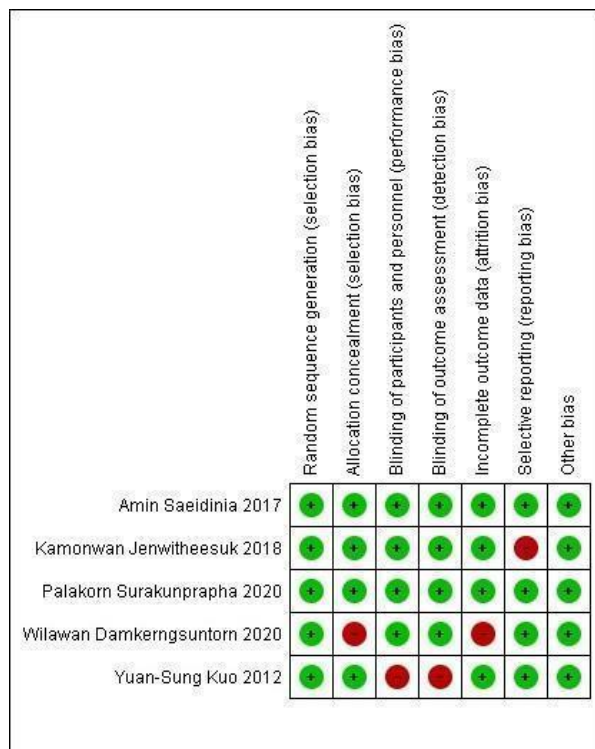


Figure 2. Risk of bias summary for the included study. Low risk of bias (+), unclear risk of bias (?), and high risk of bias (-)

Effects of interventions

The effective rate of *C. asiatica* utilization for wound healing in human from five articles were based on Wagner grade, skin erythema, re-epithelialization, VSS (vascularity, pigmentation, pliability, height) and VAS (visual acuity score).

Wagner grade evaluation

Yuan-Sung Kuo and others [19] reported a slightly reduction in Wagner grade and wound size for diabetic patients with foot ulcers. In this research, 24 patients were treated with a topical cream (WH-1) containing *P. amboinicus* and *C. asiatica* extracts or hydrocolloid fiber for 2 weeks. The improvement of Wagner grade was found in 90.9% of patients in WH-1 cream group; whereas, 70% of patients in control group had shown the improvement in Wagner grade. Wound size is one of the parameters in Wagner grade classification system, thus wound size in WH-1 cream group also reduced. However, there is no significant difference between groups for both outcomes.

Skin erythema and wound appearance

In a clinical trial research carried out by Wilawan Damkerngsuntorn and others [15], thirty participants with facial acne scars underwent a treatment with 2940 nm Er: YAG laser. Half side of the face was randomized to receive 0.05% w/w ECa 233 gel *C. asiatica* and the other side a placebo gel. The gels were applied 4 times daily for 7 days then twice daily for 3 months. The skin treated with *C. asiatica* showed statistically significant improved erythema and wound appearance at days 2, 4, and 7 (p-value < 0.05).

VSS Scores

Three trials [14, 20, 21] measured the effect of *C. asiatica* treatment on Vancouver Scar Scale (VSS). Kamonwan Jenwitheesuk and others [14] demonstrated the effect of centella cream comparing to placebo with the participants who underwent a split thickness skin graft (STSG) operation. Each intervention was applied at least 2 weeks after 14 days of epithelialization. At the end of the intervention period, only 23 patients completed the assessment. The VSS assessment was taken three times at 4, 8 and 12 weeks. It was found that pigmentation, one of the VSS parameters of experimental group at 8 and 12 weeks as well as between 4 and 12 weeks; placebo group at 12 weeks and between 4 and 12 weeks showed significant differences with p-value less than 0.05. The total VSS scores between 4 and 12 weeks of experimental group was also showed significant differences with p-value less than 0.05. However, for height in experimental group, it was worse at 4 weeks (p-value = 0.043). Amin Saeidinia and others [20] investigated the healing efficacy of Centiderm ointment, a derivative of *C. asiatica* on second-degree burn wounds when compared to silver sulfadiazine, the gold standard topical burn therapy. All VSS parameters were lower in the intervention group compared to the control group (p-value = 0.001). However, pigmentation did not reach statistical significance until day 14 of treatment (p-value = 0.001).

Palakorn Surakunprapha and others [21] utilized topical silicone gel plus 15% of herbal extract mixture (*Allium Cepa*, *Centella Asiatica*, *Aloe Vera* and *Paper Mulberry*) or placebo for 48 post-median sternotomy patients for 6 months. The scar is observed by plastic surgeons using the VSS. After 6 months all parameters in the intervention group were greater than the control group. In particular, the pliability and height were significantly greater in numbers of improvement in the intervention group than in the placebo group (p-value < 0.05). A reason for this outcome might be the effect of either silicone gel and herbal extract. Silicone gel is able to simulate the homeostasis of the stratum corneum and can also facilitate regulation of fibroblast production and reduction in collagen production. These effects help to soften the scar leading to scar reduction. Additionally,

the formation of scar can be reduced by inhibitory effect of *C. asiatica* on the expression of the transforming growth factor-beta (TGF- β) 1 and 2.

VAS Scores

The visual acuity score (VAS) was evaluated in the study of Amin Saeidinia and others [20] on burn wound. The declination of VAS score in day 3,7,14 in CA group exhibited better healing than that of the control group (SSD group) with p-value less than 0.001.

Re-epithelialization

In a clinical trial carried out by Amin Saeidinia and others [20] treated 75 patients with second-degree burn wounds on their limbs. These patients were administered topically treated once a day, with either Centriderm cream (a topical ointment containing *C. asiatica*) or 1% silver sulfadiazine cream. Re-epithelialization in the intervention group was 13.7 ± 1.48 days compared to 20.67 ± 2.02 days in the control group (p-value < 0.001). For this outcome might be the effect of *C. asiatica* on the production of vascular endothelial growth factor (VEGF) resulting by the increase in monocyte chemoattractant protein-1 (MCP-1) expression in keratinocytes and the increase in IL-1b expression in macrophages leading to wound healing acceleration.

Discussion

Wound healing effect from *C. asiatica* was mentioned in traditional medicine in many countries such as India, Sri Lanka, China and Thailand [22]. The current systemic review of *C. asiatica* for wound healing found that the herb may provide a positive effect on wound healing. The phytochemical constituents in *C. asiatica* have been used to support the claim for its therapeutic effect. Previous clinical study of ECa 233 gel composing of madecassoside 51% and asiaticoside 38% exhibited the improvement of erythema and wound appearance [15]. Asiaticoside, a triterpene constituent in *C. asiatica* has been studied for wound healing activity in normal and diabetic animal model [23]. The compound has been reported to improve wound healing process through collagen formation and angiogenesis; improve the tensile strength of the newly skin formation; inhibit the inflammatory process; improve the capillary permeability [7, 24]. Antioxidants play an important role on wound healing [25]. In animal model, asiaticoside obtained from *C. asiatica* possessed the ability to enhance antioxidant level in tissue leading to the enhancement of wound healing [26]. Previous study of asiaticoside obtained from *C. asiatica* treated with normal and keloid fibroblasts have revealed the ability of the compound to decreased fibroblast cell proliferation in a time- and dose-dependent manners; inhibit mRNA expression as well as type 1 and type 3 collagen protein expression; decrease TGF- β RI and

TGF- β RII expression; promote the expression of Smad7 protein and mRNA [27]. The increment of collagen formation may be due to vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [28]. During angiogenesis VEGF increases the vascular permeability. The mechanism by which VEGF is stimulated results from increased expression of IL-1 β and Monocyte Chemoattractant Protein-1 (MCP-1) [28]. In addition, the *C. asiatica* has anti-inflammatory effects so that it can cause the reduction in IL-1 β , IL-6 and TNF α , as well as prostaglandin E2 (PGE2) [29]. IL-1 β , IL-6 and TNF α are pro-inflammatory cytokines secreted by inflammatory cells. These substances can stimulate cyclooxygenase enzymes that convert arachidonic acid to prostaglandin, especially prostaglandin E2 [30]. PGE2 plays a role in the regulation of the immune response and blood pressure. As a result, during inflammation, PGE2 can cause swelling, redness, and pain around the wound [23]. Therefore, *C. asiatica* may decrease these substances by reducing inflammation in the affected area [31].

The current study had several limitations. The number of included studies was only 5 studies in the systematic review, were tested, varied between the studies, making comparisons between them exceedingly difficult. Therefore, it was not possible to conduct a meta-analysis to assess the effect of *C. asiatica* on the reviewed outcomes. Thereby further clinical studies are needed to evaluate the effectiveness of *C. asiatica* in wound healing.

Conclusion

Based on the five articles included in this systematic review, the therapeutic potential of *C. asiatica* in terms of its efficacy and versatility for wound healing might show the good outcome for this property. The most prominent mechanism is to increase collagen synthesis due to increased angiogenesis and its anti-inflammatory effect. Furthermore, this anti-inflammatory effect may result in reduced swelling, redness, and pain in the wound area due to the lessening of prostaglandin E2 (PGE2) and other inflammatory factors.

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