A REVIEW OF THE PHARMACOLOGICAL ACTIVITIES OF *CENTELLA ASIATICA L.* : THE POTENTIAL FOR DIABETIC FOOT ULCER THERAPY

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ABSTRACT: Patients with diabetes mellitus often experience adverse complications, one of which is diabetic foot ulcers. Administering synthetic chemical drugs and physical treatment for wound healing and tissue regeneration deficiency in hyperglycemia is considered less effective and incurs high cost if long-term treatment is given. Ineffective therapy for diabetic foot ulcers carries the high risk of amputation and death. The development of plant-derived drugs is potential to discover effective, affordable, and safe therapy. *Centella asiatica L.* (*C. asiatica)* has wound-healing activities on the skin supported by its antibacterial, anti-inflammatory, antidiabetic, and antioxidant properties. Some of these pharmacological activities are expected to synergize in the healing process of diabetic ulcers. This review aims to reveal the supporting pharmacological activities of C. asiatica in wound healing which can be the basis for developing diabetic foot ulcer therapy. This study was conducted as a literature review through searches using the keywords "*Centella asiatica*", "wound healing", "antidiabetic activity", "antibacterial activity", and "antioxidant activity" from various journal articles in NCBI, PubMed, and other journal sources. The results show that C. asiatica has the potential to be developed for diabetic foot ulcer therapy with its supporting pharmacological activities, including the antidiabetic, anti-inflammatory, antioxidant, and antibacterial properties, which will improve its effectiveness in the wound-healing process.

Keywords: *Centella asiatica L*, diabetic ulcer, wound healing

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INTRODUCTION

Patients diagnosed with diabetes mellitus frequently experience adverse complications, such as diabetic foot ulcers. Data from a systematic review reveal that the global prevalence of foot ulcer among diabetic patients ranges from 3% to 13% (1). Ineffective therapy in diabetic foot ulcers runs the great risk of amputation and death. It is reported that approximately 15-20% of diabetic foot ulcer patients undergo an amputation(2). Synthetic chemical drug administration and physical treatment for wound healing and deficiency in tissue regeneration in a hyperglycemic condition are considered less effective but costly in prolonged administration (3,4). Medicine from natural ingredients is potential to develop effective, affordable, and safe therapy. Indonesia is the second richest country in terms of biodiversity. Approximately 7500 medicinal plants have been identified(5). This indicates the existence of a national asset to be explored, researched, developed, and optimized. *C. asiatica* , one of Indonesia's native medicinal plants, has been used as medicine by Indonesian people for generations. *C. asiatica* is reported to have numerous benefits(6,7)**.**

C. asiatica has wound-healing activity on the skin reinforced by its antibacterial, anti-inflammatory, antidiabetic, and antioxidant properties(8–11). Studies prove that *C. asiatica* has chemical compounds that play an essential role in treatment due to its bioactive components, which include flavonoids, tannins, saponins, alkaloids, terpenoids, phenols, and glycosides(12). The most important bioactive component of some other active ingredients is triterpenoid saponins. Among the triterpenoid saponins are asiaticoside, centelloside, madecassoside, and asiatic acid. Saponins stimulate the production of collagen, a protein structure that plays a role in the wound-healing process(11,13). This review aims to reveal the supporting pharmacological activities of C. asiatica in wound healing which can be the basis for the development of diabetic foot ulcer therapy.

RESEARCH METHODS

This review article was conducted through literature research on various journal articles explored from NCBI, PubMed, and other journal sources on the internet that discussed antidiabetic, antimicrobial, wound healing, and antioxidant pharmacological activities. The search for literature was carried out using the keywords "*Centella asiatica*", "wound healing", "antidiabetic activity", "antibacterial activity", and "antioxidant activity". The literature search technically used a combination of keywords with Boolean operators of "OR" or "AND". The search was conducted on studies related to preclinical trials as well as clinical trials of *C. asiatica* in the wound-healing process. The articles prioritized for the review were those written in the last 10 years.

RESULTS AND DISCUSSION

BOTANICAL DESCRIPTION OF *C. ASIATICA*

C. asiatica is a wild plant originating from tropical Asia with a fairly-widespread distribution in highland and lowland areas of up to 2,500 meters above sea level. This plant prefers damp soil and adequate sunlight and is hence easily found in paddy fields, fields, plantations, yards, and roadsides with sandy soil or clay. The leaves of *C. asiatica* are green, oval with a smooth upper surface and back, serrated, slightly curved up on the edges, and hairy on the lower surface, and they have a diameter of 1-7 cm with palminerved leaf veins. The stems ohave a slightly soft/non-woody texture and reddish color at the base and green at the petiole near the leaf blade, with a taproot system. The plant also has tiny white or pink flowers with an oblong, concave shape and point to the tip(14).

CHEMICAL CONTENTS OF *C. ASIATICA*

In the leaves of *C. asiatica*, the contained phytochemical compounds include saponins, alkaloids, flavonoids, terpenoids, tannins, and steroids (15–17). Asiaticoside is a triterpenoid compound composed of 30 carbon atoms (C) as the characteristic of triterpenoids as well as glycone and aglycone (the characteristic of saponin glycosides) that are responsible for wound-healing activities as anti-inflammatory, antioxidant, antimicrobial, and collagen synthesis agents ((9,10,18–21). A Gas Chromatography – Mass Spectrophotometry (GC-MS) analysis of *C. asiatica* reveals the presence of such compounds as α-copaene, α-terpinene, β-pinene, β-elemene, bornyl acetate, and bicycloelemene. *C. asiatica* also contains some polyacetylene compounds, including 8-acetoxyfalcarinol (22). Among the different parts of the plant, *C. asiatica* leaves show the highest phenolic content (leaves = 8.13–11.7 g/100 g, roots = 6.46–10.5 g/100 g, petioles = 3.23–4.91 g/100 g) (23). (23)(23)(23)(23)(23)(23)(23)(Torbati et al., 2021) Tannins, fatty oils, and resinous substances are detected from the alcohol extract. Important terpenoid components, such as trans-β-farnesene, β-caryophyllene, and germacrene-D, are also identified from the ether extract. The key marker compounds are asiaticoside, madecassoside, and asiatic acid. The ethanol extract is rich in amino acids especially glutamic acid, serine, alanine, threonine, aspartic acid, histidine, and lysine(24). Hydrocotylin is also detected in *C. asiatica* simplicia. The plant is rich in vitamins A (442 µg/100 g), B1 (0.09 mg/100 g), B2 (0.19 mg/100 g), B3 (0.1 mg/100 g), and C (48.5 mg/100 g) as well as minerals such as Na (107.8 mg/100 g), K (345 mg/100 g), Ca (174 mg/100 g), Mg (87 mg/100 g), P (17 mg/100 g), and Fe (14.86 mg/100 g). Such minerals as K, Ca, S, Mg, and P (31.82, 12.83, 4.35, 3.45, and 2.90 mg/g according to their corresponding dry weights) are determined by using an atomic absorption spectrophotometer (AAS) (25,26) **Figure 1** shows the structure of asiaticoside, the key marker compound, on MarvinSketch 18.22.

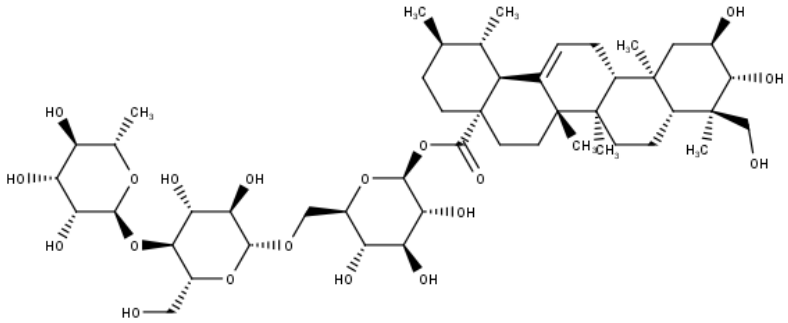

Figure 1. Chemical structure of asiaticoside

PHARMACOLOGICAL ACTIVITIES OF *C. ASIATICA* IN THE WOUND-HEALING

ANTIHYPERGLYCEMIC ACTIVITY *OF C. ASIATICA*

Diabetes mellitus (DM) is a non-communicable metabolic disease characterized by increased glucose levels in the blood (hyperglycemia) due to reduced secretion of the hormone insulin, insulin resistance, or both(27,28). The treatment process for diabetic foot ulcers as a diabetes complication suggests that it is important to control blood glucose to improve wound healing and reduce aggravation. Although a recent Cochrane review found it challenging to conclude whether intensive glycemic control has a positive or detrimental effect on the treatment of diabetic foot ulcers due to the lack of RCTs, some observational studies have found a positive correlation between blood glucose control and wound healing. In addition, another Cochrane review assessing the effect of glycemic targets on type-2 diabetes found that patients with intensive glycemic control had a 35% reduction in the risk of lower-extremity amputation(29). Studies of the antidiabetic effect of C. asiatica is presented in **Table 1.**

Table 1. In-vivo studies of the antidiabetic activity of C. *asiatica*

Compound	Test Subject	Result	Reference
Methanol Extract	Male Sprague–Dawley rats	↓ blood glucose, ↓ food and water intake, ↓ ALT, ↓ AST, ↑ PFK, ↑ GS, ↑ GP, ↑ glycogen content	(30)
Methanol Extract	Male Sprague–Dawley rats	↓ blood glucose, ↑ GSH, ↑ GST, ↑ GPX, ↓ MDA, ↓ TNF-a, ↓ IFN-γ, ↓ IL-10	(31)
Ethanol extract	Male Wistar rats	↓ blood glucose	(32)
Aqueous extract	Male and female Wistar rats	↓ blood glucose	(33)
Ethanol extract	Long evan type	Inhibition of intestinal disaccharidase enzymes and α-amylase and by glucosefibre binding	(34)
Ethnol extract SNEDDS	Zebrafish	The antidiabetic activity test found a 69.90% decline in FBG levels in 100mg/2 L SNEDDS and 72.20% in 200 mg/2 L SNEDDS.	(35)
Ethanol extract	Rats	Reduction of SOD1 and SOD3 promotes the downregulation of nephrin and upregulation of TRPC6 mRNA expressions in rat glomerular kidney.	(36)

MDA = malondialdehyde, GSH = glutathione, GST = glutathione s-transferase, GPX = Glutathione Peroxidase-1, TNF-α = tumor necrosis factor α, ALT = alanine transaminase, AST = aspartate transaminase, PFK = phosphofructokinase, GS = glycogen synthase, GP = glycogen phosphorylase, IFN-γ = Interferon-gamma, IL-10 = Interleukin-10, FGB = Fasting Blood Sugar

Current evidence suggests that *C. asiatica* extract and asiatic acid can lower blood glucose levels, improve insulin resistance, inhibit weight gain, improve inflammation, and improve oxidative stress. The mechanism of antihyperglycemic activity of *C. asiatica* is to inhibit the enzyme α-glucosidase. The compound of *C. asiatica* that plays a role in such activity is quercetin(37). In addition to inhibiting α-glucosidase, *C. asiatica* is reported to have antihyperglycemic effects by increasing the glycolytic enzyme activity; increased glycogenesis in the skeletal muscle can help reduce the build-up of glucose in the blood(30). These results indicate the benefit of *C. asiatica* extract to control blood glucose. In addition, inflammatory response can lead to type-2 diabetes mellitus by inducing insulin resistance. Inflammatory response is aggravated by hyperglycemia while the inflammatory response per se can aggravate hyperglycemia. Therefore, targeting inflammatory pathways can be a potential strategy to prevent and control diabetes(21).

ANTI-INFLAMMATORY AND WOUND-HEALING ACTIVITY OF *C. ASIATICA*

Wound healing is the process of repairing the structure of damaged skin tissue (38). In general, there are four phases of the wound-healing process, which include the coagulation phase, the inflammatory phase, the proliferative and migratory phase (tissue formation), and the remodeling phase. Wound healing is a physiological process to recover the skin and repair damaged tissue. Skin wound healing occurs in four phases: hemostasis, inflammation, proliferation, and remodeling. Asiaticoside has been found to promote the migration rate of normal human skin cells, attachment, and growth in an in-vitro wound-healing model.

The active compounds of *C. asiatica* possess some properties that can be utilized as herbal medicine. *C. asiatica* is reported to have numerous benefits and properties related to antimicrobial, antioxidant, wound-healing, anti-inflammatory, and antihyperglycemic activities. Triterpenoids improve mental functions and give a calming effect. In addition, this compound can revitalize blood vessels and therefore increase blood circulation to the brain. Asiaticoside is part of triterpenoids that can strengthen skin cells and improve skin cell repair, stimulate blood cells and the immune system, and function as natural antibiotics. Meanwhile, brahmoside is a compound that can improve blood flow and contain important proteins for the brain cells(39). *C. asiatica* has empirically proved to have wound-healing activity, making it such a potential source to develop wound-healing compounds.

Wound healing is a complex biological process involving coagulation, inflammation, cytokine production, cell migration, proliferation and differentiation, angiogenesis, synthesis, and remodeling of the extracellular matrix (including collagen production and deposition). Collagen type I and collagen type III are the key components of the extracellular matrix of the skin. Both types play an important role in the wound-healing process. This results in epithelial cell proliferation and wound contraction. Asiaticoside (AS), a triterpene glycoside isolated from *C. asiatica*, has been found to have anti-inflammatory effects and is used as a clinical wound-healing agent that promotes fibroblast proliferation and collagen synthesis (40,41). Research on the anti-

inflammatory and wound-healing activity of *C. asiatica* can be seen in **Table 2 and Table 3.** A standardized extract of *C. asiatica* induces keratinocyte migration and promotes wound healing through the activation of FAK, AKT, and MAPK signaling pathways (42). According to the research findings, *C. asiatica* has proved to play an active role in the wound-healing process and regulation of inflammatory agents.

Table 2. In-vitro studies of wound healing *(C. asiatica)*

Compound	Testing	Results	Reference
Asiaticoside	Human skin fibroblasts	Increased migration and proliferation of fibroblasts; increased synthesis of the extracellular matrix	(43)
Asiaticoside	Human periodontal ligament cells	Increased mRNA and proteins from fibronectin and collagen type I; decreased expression of metalloproteinase-I mRNA	(44)
Water extract	Wound-healing model of rabbit corneal epithelial cells	Increased cell migration; changes in proliferation and cell cycle	(45)

Table 3. In-vivo studies of wound healing *(C. asiatica L.)*

Compound	Testing	Results	Reference
Hexane, methanol, ethyl acetate, and water extracts	Incisions and burns, topical application on rats	Improved wound healing	(46)
Asiaticoside	Rats treated with LPS, oral administration in rats	Increased TNF-α, IL-6, COX-2, PGE2, liver myeloperoxidase, IL-10; up-regulation of heme oxygenase-1	(47)
Methanol extract of *C. asiatica*	Skin wounds in male rats	Improved wound healing	(48)

Asiaticoside	Skin wounds in male rats	↑ skin flap survival, ↓ tissue moisture content, ↑ SOD, ↓ MDA, ↓ TNF-a, ↓ IL-6, ↓ neutrophil density, ↑ neovascularization, ↑ VEGF, ↓ TNF-a, ↓ IL-6, ↓ IL-1b, ↑ flap blood flow	(49)
Asiaticoside-rich hydrogel formulation	Wounds in rabbits	↓ wound size, ↑ epithelialization period	(20)
C. asiatica extract	Tongue wounds in male rats	↓ MPO, ↓ MDA, ↑ degree of re-epithelialization, ↑ CD31	(50)
Raw-extract of *C. asiatica*	Sprague Dawley rats	Significantly suppressed the level of pro-inflammatory cytokine/mediators and oxidative stress	(51)

IL-6 = Interleukin 6, MPO = myeloperoxidase, COX-2 = cyclooxygenase-2, PGE2 = Prostaglandin E2, IL-10 = Interleukin 10, SOD = superoxide dismutase, VEGF = Vascular endothelial growth factor, CD31 = cluster of differentiation 31

The wound-healing process is supported by asiaticoside which can improve the repair and strengthen the skin cells. The triterpene compounds, including asiatic acid, madecassic acid, asiaticoside, and madecassoside, are responsible for wound healing, and this has been evidenced in in-vitro and in-vivo studies. Asiaticoside induces the synthesis of type I collagen in dermal fibroblasts and improves the antioxidant level of wounds. Antioxidants can reduce the oxidative stress of wounds and accelerate wound healing(52). Asiaticoside can stimulate the synthesis of type I collagen in human dermal fibroblasts through the activation of TGF-β receptor I kinase SMAD-independent pathways, which becomes the basis for understanding plant-derived bioactive molecules in the wound-healing process. The mechanism of action of asiaticoside is to promote fibroblast proliferation and extracellular matrix (ECM) synthesis which play an important role in the wound-healing process (18). In addition, asiaticoside facilitates the wound-healing process by increasing the level of peptic hydroxyproline component, tensile strength, collagen synthesis, angiogenesis, and epithelialization in the remodeling phase of wound healing (18,53,54). This compound can also increase the antioxidant levels to promote wound healing ((54,55)act as an antibacterial agent to prevent infections(56)accelerate epidermal formation, and inhibit the inflammatory phase in hypertrophic scars and keloids. The asiatic acid in *C. asiatica* can promote wound healing by inhibiting inflammation, stimulating angiogenesis, reducing oxidative stress of wounds, and inducing vasodilation and collagen synthesis in granulation tissue to promote fibroblast proliferation in wounds. Madecassoside plays a role in stimulating cell growth and producing an anti-inflammatory effect(57). Madecassic acid increases the synthesis of type III procollagen which accelerates and improves wound healing (58). *C. asiatica* extract has proved to affect cell growth and proliferation in wounded tissues.

ANTIOXIDANT ACTIVITY OF C. ASIATICA

Oxidative stress is mainly caused by lipid peroxidation, which is considered the key indicator of the pathogenesis and development of type-2 diabetes mellitus. Oxidative stress induces microvascular and macrovascular complications (59). Reactive Oxygen Species (ROS) are oxygen-derived molecules mainly produced by the respiratory chain in the mitochondria, some of which include hydrogen peroxide (H_2O_2), superoxide anion (O^-2), and peroxide (O^{2-}_2). Such oxidizing agents contribute to cell damage ((60–62)but conversely play a valuable role and particularly important role in the preparation of the normal wound-healing response (63). Therefore, an appropriate balance between low and high ROS levels is crucial. Low levels of ROS are beneficial to protecting tissue against infections and stimulating effective wound healing through the production of cell survival signaling (64); however, excessive presence of ROS results in oxidative stress that induces cell damage and pro-inflammatory status (65).(65)(65)(65)(64)(63)(62)(61)(Ponugoti et al., 2013) Redox imbalance takes place when ROS levels exceed the capacity of endogenous antioxidants to dysregulate the wound-healing process(66). Oxidative stress appears in cells and tissue through increased production of reactive oxygen species (ROS) and/or from decreased antioxidant defense systems. The efficiency of defense mechanisms in diabetes is altered, and ineffective management of free radicals is likely to play an important role in defining tissue damage. There is no distinct limit to the level of ROS in tissue, but a range from 100 μM to 250 μM for hydrogen peroxide as the most common ROS is recommended in normal wounds [10,13]. In addition, some studies suggest that 10 μM of hydrogen peroxide can act as a chemoattractant and enhance the proliferation of fibroblasts and endothelial cells, and 100 μM of it can stimulate angiogenesis through the production of vascular endothelial growth factor, but 500 μM of H_2O_2 can induce pro-inflammatory status via the production of macrophage

inflammatory protein-1 α [14]. Antioxidants are chemical compounds that can donate their electrons to other molecules, such as ROS, thus preventing them from taking the electrons of other important biological molecules, including proteins or DNA [15]. Based on the mechanism of action, there are two types of antioxidant compounds: non-enzymatic and enzymatic. Non-enzymatic antioxidants are compounds with low molecular weight, such as vitamin E, vitamin C, glutathione, and flavonoids. Meanwhile, enzymatic antioxidants include superoxide dismutase, catalase, glutathione peroxidase, and thioredoxin-1 and -2, [15,16]. Antioxidants catalyze a series of complex reactions to convert ROS into more stable molecules, such as H_2O and O_2; consequently, they are referred to as ROS scavengers. Regulation of redox balance by modulating ROS and antioxidant levels has recently become a new therapeutic target. Antioxidant substances that maintain non-toxic ROS levels in wound tissue can promote wound healing [15]. Therefore, antioxidant activity is important in the process of diabetic foot ulcer therapy. *C. asiatica* extract is likely to improve oxidative stress. *C. asiatica* increases the activity of GSH, CAT, and SOD, thereby enhancing the enzymatic antioxidant system. Research on the antioxidant effects of *C. asiatica* is shown in **Table 4.**

Table 4. Studies of the antioxidant activity in *C. asiatica*

Compound	Testing	Results	Reference
Ethanol extract	DPPH Testing	83% inhibition of free radical activity at a concentration of 1 mg/mL	(54)
Ethanol extract and aqueous extract	DPPH Testing	IC50 of 100% ethanol extract of C. asiatica, 50% ethanol extract of C. asiatica, and water extract of C. asiatica = 35.6±1.3 μg/ml, 7.1±1.5 μg/ml, and 10.3±1.2 μg/ml, respectively	(67)
Ethanol extract	DPPH Testing	IC50 = 78.20 μg/ml	(68)
Ethanol extract	DPPH and SOD testing	IC50 = 125 μg/ml; proved to increase SOD levels in test animals	(69)
Fraction from ethanol extract	SOD, GSH-Px, and MDA observation	Increased SOD and GSH-Px activity; lowered MDA levels	(61)
Ethanol extract	CAT,GPx1, SOD1, and SOD2 observation	Upregulation of cellular antioxidant enzymes appeared to be major contributor for the protective effects of callus extract against oxidative stress.	(70)

ANTIBACTERIAL ACTIVITY OF *C. ASIATICA*

When there is a wound, it carries the high risk of infection for patients. In patients with diabetes mellitus, it is aggravated by the presence of hyperglycemia. *C. asiatica* contains various biochemical compounds, especially flavonoids, with antimicrobial properties. Flavonoids have been known to possess antimicrobial characteristics since they have numerous cellular targets, including inhibiting the formation of microbial nucleic acids, function of cytoplasmic membrane, and microbial metabolism(71).

Diabetic foot problems, such as ulceration, infection, and gangrene, are the common causes of hospitalization for diabetic patients. Regular treatment of diabetic foot is given to any forms of abnormality in the foot due to diabetes mellitus. The main contributing factor in the presence of diabetic foot comes from a combination of autonomic neuropathy and somatic neuropathy, vascular insufficiency, and infection. Diabetic foot among inpatients is generally caused by a negligible minor trauma. This has led to continuous transmission of infection, and the disability rate becomes higher .

The standards for diabetic foot ulcer management include prevention, education to patients, glycemic control, wound debridement, infection management, revascularization procedure as per indication, ulcer removal, and reconstructive surgery, if necessary. Other methods or additional therapy can be beneficial, such as

hyperbaric oxygen therapy, use of advanced wound care products, and negative pressure wound therapy. Infection in the wound can aggravate the ulcer condition; therefore, it is important to manage infection in the wound-healing process (72).

A study of 213 samples of patients with wounds found that the most-commonly detected bacterial species were Staphylococcus aureus (37%), followed by Pseudomonas aeruginosa (17%), Proteus mirabilis (10%), Escherichia coli (6%), and Corynebacterium spp. (5%). Polymicrobial infection was found in 59 samples (27.1%). Hence, agents with antibacterial activity are advantageous to the process of developing diabetic foot ulcer therapy(73). Control of infection is aimed at reducing the poor prognosis of diabetic foot ulcers. Studies of the antibacterial activity of C. asiatica can be seen in **Table 5.** The reported antibacterial activity in four types of extract, assessed based on the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC), show the potential of *C. asiatica* in combating the bacteria commonly found in wounds. From the obtained MIC and MBC values, it was found that the most intense activity was shown in water extract.

Table 5. Antimicrobial activity of *C. asiatica* against the bacteria frequently found in wounds

	Methanol Extract		Ethyl Acetate Extract		Water Extract		Acetone Extract		Ref.
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	
Staphylococcus aureus	2.5	10	1.25	5	5	>10	1.25	5	(74)
Pseudomonas aeruginosa	5	>10	10	>10	10	>10	5	>10	
Proteus mirabilis	2.5	>10	>10	>10	>10	>10	5	>10	
Escherichia coli	1.25	5	5	>10	>10	>10	0.63	5	

*MIC and MBC in mg/mL units

CLINICAL TRIALS OF *C. ASIATICA*

A large majority of the clinical studies of *C. asiatica* are reported on alcohol extract or water extract. TECA (Titrated Extract of *C. asiatica*) and TTFCA (Total Triterpenic Fraction of *C. asiatica*) consist of a combination of asiatic acid (30%), madecassic acid (30%), and asiaticoside (40%). TTF (Total Triterpenic Fraction) extract is comprised of *C. asiatica* and madecassic acid (60%) in combination with asiaticoside (40%). Both in-vivo clinical studies and human cell monolayer culture experiments conclude that asiatic acid affects collagen synthesis. Local application of triterpenoid fractions for wound healing emphasizes the role of asiaticoside in increasing antioxidant levels (enzymatic and nonenzymatic) to accelerate wound healing.

In the case of vascular injury, thrombosis, acute myocardial infarction, and other peripheral vascular diseases, a higher number of endothelial cells is detected. One study reported that patients with post phlebitic syndrome (PPS) showed a greater number of endothelial cells compared to normal subjects. During a three-week treatment with the triterpenic fraction of *C. asiatica* (CATF), PPS patients receiving 90 mg of CATF daily in three divided doses showed a statistically significant decrease in the number of endothelial cells, thus indicating the effectiveness of *C. asiatica* ((75). *C. asiatica* extract was tested in 94 patients suffering from lower extremity venous insufficiency. The patients were divided into three groups, each treated with TECA (120 mg/day, 60 mg/day, or placebo) for two months. A statistically significant difference in favor of the TECA group was observed in the parameters examined for lower extremities and edema; in addition, an overall evaluation showed a positive result for the group treated with TECA compared to that with placebo(75).

CATF has proved to be effective on microcirculation and capillary permeability. Fifty-two patients with venous hypertension (pressure greater than 42 mmHg) were divided into three groups, each treated with 60 mg/day, 30 mg/day, or placebo. Ten additional control subjects were administered with 60 mg of CATF per day. After four weeks of treatment, significant improvement was observed in a concentration-dependent manner on the parameters tested, including the filtration rate, ankle edema, and ankle circumference. No significant changes were found among the placebo and control subjects treated with CATF (76). The recent clinical trials related to C. asiatica wound-healing activity are presented in **Table 6.**

Table 6. Reported clinical trials of *C. asiatica* relating to wound healing

Compound	Test Subjects	Quantity	Results	Reference
3 x 100 mg of AS	Diabetic patients with foot wound	170	↑ Wound contraction, ↑ Wound granulation	(77)
3% topical Centiderm	Patients with burn wound	75	↓ VSS score, ↓ VAS score, ↑ Re-epithelialization, ↓ Healing time, ↓ Infection, ↓ Pigmentation	(78)
2 × 60 mg of oral + 3 g of topical C. asiatica	Patients with chronic anal fissure	98	↓ Pain (VAS scores)	(79)
Topical 0.05% ECa 233	After laser treatment	30	↓ Erythema, ↑ Wound appearance, ↑ Epithelialization	(80)

AS = asiaticoside, ECa 223 = 51% madecosside and 38% asiaticoside, SSD = Silver Sulfadiazine, TECA = Titrated Extract from C. asiatica, TTFCA = total triterpenoid fraction of C. asiatica, VAS = visual acuity score, VSS = Vancouver Scar Scale, ↑ = increased, ↓ = decreased

CONCLUSION

Based on the literature review conducted, it can be concluded that C. asiatica has the potential to be developed for diabetic foot ulcer therapy with such supporting pharmacological activities as antidiabetic, anti-inflammatory, antioxidant, and antibacterial. These properties have been preclinically and clinically proven, making it potential to be the basis for further development of nature-based pharmaceutical preparations to treat wounds in diabetic patients.

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Table 1. In-vivo studies of the antidiabetic activity of C. *asiatica*

Compound	Test Subject	Result	Reference
Methanol Extract	Male Sprague–Dawley rats	↓ blood glucose, ↓ food and water intake, ↓ ALT, ↓ AST, ↑ PFK, ↑ GS, ↑ GP, ↑ glycogen content	(30)
Methanol Extract	Male Sprague–Dawley rats	↓ blood glucose, ↑ GSH, ↑ GST, ↑ GPX, ↓ MDA, ↓ TNF-a, ↓ IFN-γ, ↓ IL-10	(31)
Ethanol extract	Male Wistar rats	↓ blood glucose	(32)
Aqueous extract	Male and female Wistar rats	↓ blood glucose	(33)
Ethanol extract	Long evan type	Inhibition of intestinal disaccharidase enzymes and α-amylase and by glucosefibre binding	(34)
Ethnaol extract SNEDDS	Zebrafish	The antidiabetic activity test found a 69.90% decline in FBG levels in 100mg/2 L SNEDDS and 72.20% in 200 mg/2 L SNEDDS.	(35)

MDA = malondialdehyde, GSH = glutathione, GST = glutathione s-transferase, GPX = Glutathione Peroxidase-1, TNF-α = tumor necrosis factor α, ALT = alanine transaminase, AST = aspartate transaminase, PFK = phosphofructokinase, GS = glycogen synthase, GP = glycogen phosphorylase, IFN-γ = Interferon-gamma, IL-10 = Interleukin-10, FGB = Fasting Blood Sugar

Table 2. In-vitro studies of wound healing *(C. asiatica)*

Compound	Testing	Results	Reference
Asiaticoside	Human skin fibroblasts	Increased migration and proliferation of fibroblasts; increased synthesis of the extracellular matrix	(43)
Asiaticoside	Human periodontal ligament cells	Increased mRNA and proteins from fibronectin and collagen type I; decreased expression of metalloproteinase-I mRNA	(44)
Water extract	Wound-healing model of rabbit corneal epithelial cells	Increased cell migration; changes in proliferation and cell cycle	(45)

Table 3. In-vivo studies of wound healing *(C. asiatica L.)*

Compound	Testing	Results	Reference
Hexane, methanol, ethyl acetate, and water extracts	Incisions and burns, topical application on rats	Improved wound healing	(46)
Asiaticoside	Rats treated with LPS, oral administration in rats	Increased TNF-α, IL-6, COX-2, PGE2, liver myeloperoxidase, IL-10; up-regulation of heme oxygenase-1	(47)
Methanol extract of *C. asiatica*	Skin wounds in male rats	Improved wound healing	(48)
Asiaticoside	Skin wounds in male rats	↑ skin flap survival, ↓ tissue moisture content, ↑ SOD, ↓ MDA, ↓ TNF-a, ↓ IL-6, ↓ neutrophil density, ↑ neovascularization, ↑ VEGF, ↓ TNF-a, ↓ IL-6, ↓ IL-1b, ↑ flap blood flow	(49)
Asiaticoside-rich hydrogel formulation	Wounds in rabbits	↓ wound size, ↑ epithelialization period	(20)
C. asiatica extract	Tongue wounds in male rats	↓ MPO, ↓ MDA, ↑ degree of re-epithelialization, ↑ CD31	(50)

IL-6 = Interleukin 6, MPO = myeloperoxidase, COX-2 = cyclooxygenase-2, PGE2 = Prostaglandin E2, IL-10 = Interleukin 10, SOD = superoxide dismutase, VEGF = Vascular endothelial growth factor, CD31 = cluster of differentiation 31

Table 4. Studies of the antioxidant activity in *C. asiatica*

Compound	Testing	Results	Reference
Ethanol extract	DPPH Testing	83% inhibition of free radical activity at a concentration of 1 mg/mL	(54)
Ethanol extract and aqueous extract	DPPH Testing	IC50 of 100% ethanol extract of C. asiatica, 50% ethanol extract of C. asiatica, and water extract of C. asiatica = 35.6±1.3 μg/ml, 7.1±1.5 μg/ml, and 10.3±1.2 μg/ml, respectively	(67)
Ethanol extract	DPPH Testing	IC50 = 78.20 μg/ml	(68)
Ethanol extract	DPPH and SOD testing	IC50 = 125 μg/ml; proved to increase SOD levels in test animals	(69)

Fraction from ethanol extract	SOD, GSH-Px, and MDA observation	Increased SOD and GSH-Px activity; lowered MDA levels	(61)

Table 5. Antimicrobial activity of *C. asiatica* against the bacteria frequently found in wounds

	Methanol Extract		Ethyl Acetate Extract		Water Extract		Acetone Extract		Ref.
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	
Staphylococcus aureus	2.5	10	1.25	5	5	>10	1.25	5	(74)
Pseudomonas aeruginosa	5	>10	10	>10	10	>10	5	>10	
Proteus mirabilis	2.5	>10	>10	>10	>10	>10	5	>10	
Escherichia coli	1.25	5	5	>10	>10	>10	0.63	5	

*MIC and MBC in mg/mL units

Table 6. Reported clinical trials of *C. asiatica* relating to wound healing

Compound	Test Subjects	Quantity	Results	Reference
3 x 100 mg of AS	Diabetic patients with foot wound	170	↑ Wound contraction, ↑ Wound granulation	(77)
3% topical Centiderm	Patients with burn wound	75	↓ VSS score, ↓ VAS score, ↑ Re-epithelialization, ↓ Healing time, ↓ Infection, ↓ Pigmentation	(78)
2 × 60 mg of oral + 3 g of topical C. asiatica	Patients with chronic anal fissure	98	↓ Pain (VAS scores)	(79)
Topical 0.05% ECa 233	After laser treatment	30	↓ Erythema, ↑ Wound appearance, ↑ Epithelialization	(80)

AS = asiaticoside, ECa 223 = 51% madecosside and 38% asiaticoside, SSD = Silver Sulfadiazine, TECA = Titrated Extract from C. asiatica, TTFCA = total triterpenoid fraction of C. asiatica, VAS = visual acuity score, VSS = Vancouver Scar Scale, ↑ = increased, ↓ = decreased