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A comprehensive review on *Thankuni* (*Centella asiatica*) as an herbal remedy in diabetes mellitus and wound healing

Dr. Sreya Sen and Soumam Dutta

Abstract
Thankuni or *Centella asiatica* (CA) is a nutritionally rich and traditionally revered medicinal herb. It contains many bioactive phytochemicals, namely Asiatic acid, Asiaticoside, Madecassic acid, Madecassoside etc. The herb possesses anti-oxidant, anti-inflammatory, anti-hyperglycemic and anti-ulcer properties. Such effects may be useful for the treatment of diabetes mellitus and its complications. Wound healing may also be promoted by such properties. Thus the present article targets to summarize the role of *Thankuni* in the treatment of diabetes and wound healing and highlight the possible mechanisms underlying such effects. Relevant articles were identified using PubMed and Google Scholar. Other authentic sources were also used. CA may stimulate insulin secretion, inhibit carbohydrate digestion, absorption and regulate the major metabolic pathways of carbohydrate in the body leading to normoglycaemia. Additionally it has the ability to promote wound healing and inhibit scar tissue formation. Such evidences corroborate the effectiveness of CA for treating these conditions.

Keywords: Asiatic acid, madecassic acid, triterpenes, hyperglycemia, granulation tissue

Introduction
Herbal remedies are being used by human beings from ancient time period. They solely relied on various medicinal herbs and spices for their treatment before the modern medicine came into existence. Amongst the numerous medicinal herbs mentioned in the Ayurveda, *Centella asiatica* (CA), commonly known as *Thankuni* in West Bengal, India, has perhaps the most versatile use. It is also popularly known as *Mandukaparni* since its leaves resemble the shape of a frog. Mention of CA can be found in *Atharvaveda*, *Matsyapurana*, *Agnipurana*, *Shathpathbrahmana* and *Kaushiksutra*. In *Charaka Samhita* it is classified as *Vayastapana mahakashaya* (drug for maintaining vitality and managing age related disorders), *Tikta skandha* (drug having bitter taste), *Shaka varga* (group of vegetables), *Medhya rasayana* (nootropic herb), *Brahmarasayana* (rejuvenator). In *Susruta Samhita* it is mentioned as a *Pathya Shaka* (dietary vegetable), *Kushtha Chikitsa* (treatment of leprosy), *Mahapanchmoolasava* and *Medhayushkamiya Rasayana* (enhancer of intellect and longevity). In *Ashtanga Hridaya* it is mentioned under *Shaka varga* (group of vegetables), *Kasa Chikitsa* (treatment of cough) and *Rasayana Prakarana* (methods to rejuvenate seven humors). *Paryaya padaani* mentions it as a *Mahushadhi* (herb having many uses). [1, 2] *Bhavaprakash Nighantu* describes CA as a *Mehaghna* (Anti-hyperglycemic). [3] Countless scientific studies on this plant have proven its medicinal and dietary qualities. CA is found to possess antioxidant, [4] anti-inflammatory, [5] anti-hyperglycemic, [6] and anti-ulcer [7] properties.
In 2019, the worldwide prevalence of diabetes mellitus is found to be 9.3% (463 million people) which by 2030 may rise to 10.2% (578 million) and by 2045 may increase to 10.9% (700 million). [8] According to the National Family Health Survey (NFHS)-4 (2015-16) the total prevalence of high blood sugar among Indian adults (15-49 years) are 8% and 5.8% among men and women respectively. The prevalence of very high blood sugar among men and women are 3.9% and 2.8% respectively. [9]
Healing of wounds, burns, ulcers and scars is another challenging task in the clinical setting. Wound healing process is further problematic in patients with diabetes due to wound hypoxia, ischaemia, impaired angiogenesis, oxidative stress and increased risk of infection. [10] Thus the current study aims to provide an updated review on the potential use of *Thankuni* or CA for treating diabetes mellitus and its role in wound healing.

Aims and Objectives
1. To study scientific literatures on the Ayurvedic herb CA.

2. To study the beneficial effect of CA in diabetes mellitus as suggested from ancient age.
3. Also to study the effect of CA on wound healing, a common complication of diabetes.

Methodology

The scientific studies highlighting the role of *Centella asiatica* on blood glucose levels, diabetes and wound healing were identified through literature search. The searchers were conducted using PubMed and Google Scholar. Search items were '*Centella asiatica*', 'Asiatic acid', 'Madecassic acid', 'Diabetes' and 'Wound'. 'AND' statement was used for combining search items. Articles from 2000-2020 were included for reviewing. Additionally the reference sections of the selected articles and relevant doctoral dissertations of Department of Home Science, University of Calcutta were searched.

Details of the Plant

Thankuni or CA is an herbaceous, perennial, flowering plant native to India, Indonesia, Sri Lanka, South Pacific, Japan, China and South Africa. This plant generally grows up to seven thousand feet in damp and shady places. It can be commonly found in the banks of streams, rivers, ponds and irrigated fields. It can also be seen in rocky areas or along stone walls at elevations of around two thousand feet in India and Sri Lanka. [11] It usually grows up to a height of 15-25 cm and is odourless, tasteless or sometimes little bitter. It has small fan shaped green leaves. The colour of the flowers is white or pale purple to pink. The fruits are small in size and oval in shape. For therapeutic purposes, the leaves and stems are commonly used. The systematic classification (Taxonomy) of CA is mentioned in Table-1.

Table 1: Botanical Classification of *Centella asiatica* [12]

Classification	Name
Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Apiales
Family	Apiaceae
Genus	*Centella* L.
Species	*Centella asiatica* (L.) Urb.

100 g of CA leaves contain 34 Kcal, 6.9 g carbohydrates, 1.6 g protein, 0.6 g fat, 89.3 g water, 1.6 g ash and 2 g fibre. The mineral content includes 170 mg calcium, 30 mg phosphorus, 3.1 mg iron, 156.37mg sodium, 414 mg potassium, 2.25 mg zinc and 0.19 mg copper per 100 gm. The vitamin content includes 6.58 mg beta carotene, 0.15 mg thiamine, 0.14 mg riboflavin, 1.2 mg niacin and 4 mg ascorbic acid per 100 gm. [13, 14] The primary active components present in CA are saponins like asiatic acid, asiaticosides, madasiatic acid and madecassosides. Other compounds include brahmoside, brahminoside, thankuniside, isothankuniside, centelloside and its derivatives. [15]

Potential Role of *Centella asisatia* in Diabetes mellitus

Several plants and herbs have shown positive results in treating diabetes mellitus (DM). The exact mechanisms are not well known in many cases. The presence of certain bioactive compounds like polyphenols, flavonoids, glycosides, terpenoids etc explain their role in the prevention and management of DM. CA contains many phytochemicals out of which Asiatic acid (AA) shows a promising role. Ramachandran *et al*. (2013) in their study found that AA (5, 10, 20 mg/kg, oral administration for 45 days) can efficiently reverse the elevated blood sugar, glycated hemoglobin, glucose-6-phosphatase, fructose-1, 6-bisphosphatase levels and reduced hemoglobin, circulating insulin, hexokinase, glucose-6-phosphatedehydrogenase, pyruvate kinase and glycogen content in streptozotocin (STZ)-induced diabetic rats to near normal levels. [16] The authors in another study found anti-hyperlipidaemic activity of AA in addition to anti-diabetic properties. AA appeared to reduce 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A reductase (HMG-CoA reductase) activity and improve lipid profile in STZ-induced diabetic rats. [17] AA also reduced islet cell fibrosis in type 2 diabetic animal model at a dose of 25mg/kg for four weeks. [18]

***In vitro* Studies with CA**

Loh *et al*. (2011) evaluated the effect of hexane and dichloromethane extract of CA on α-Amylase, α-Glucosidase and Angiotensin I-Converting Enzyme (ACE-I) inhibition. Dichloromethane extract was more efficient to increase α-Amylase inhibition whereas hexane extract was more efficient to increase the inhibition of α-Glucosidase and ACE-I. These properties may be helpful in hyperglycaemia and hypertension. [19] Kabir *et al.* (2014) further found that ethanolic extract of CA can inhibit intestinal disaccharidase and α-Amylase. The dietary fiber present in CA can bind with glucose thereby limiting its absorption. [20]

***In vivo* Studies with CA**

Sen *et al*. (2009) in their experiment used two groups of normal rats. Both were maintained on a standard laboratory diet while one group received a smooth paste of fresh CA leaves at a dose of 150 mg/kg for fifteen days. They observed a significant ($p<0.05$) decrease in blood glucose level and a significant ($p<0.001$) increase in liver glycogen level in the CA treated group as compared to the non-treated group. [14] Ethanolic extract of CA at a dosage of 300 mg/kg per day for four weeks reduced blood glucose levels of low dose STZ induced obese-diabetic rats fed with a high fat diet significantly ($p<0.001$). There was also an increase in circulating insulin and decrease in cholesterol, Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) levels comparable to the normal group fed with a normal diet. CA treatment increased glycolysis, reduced neoglucogenesis and enhanced Tri Carboxylic Acid (TCA) cycle. [21]

Potential Role of *Centella asisatia* in Wound Healing

Wound healing is a natural physiological process which occurs when a tissue is injured. The process is very complex and involves interplay between numerous mediators, cytokines, cells and vascular system. The mechanism of wound healing can be categorized in three distinct phases. The first phase is the inflammatory phase which is characterised by hemostasis, chemotaxis of inflammatory cells (e.g. neutrophils, monocytes, lymphocytes) and increased vascular permeability which closes the wound, prevents further damage, removes bacteria, cellular debris and promotes cellular migration. The second phase is known as the proliferative phase where granulation tissue is formed, re-epithelialization and neovascularization take place. Finally in the maturation or remodelling phase excess collagen is

degraded and wound contraction occurs. The wound strengthens as it matures. [22] Numerous medicinal plants and herbs are found to possess anti-oxidant, anti-inflammatory, anti-microbial, analgesic properties which support their wound healing actions. The phytochemicals like polyphenols, flavonoids, saponins, triterpenoids, sterols, tannins promote healing of wounds. [23] CA is studied widely for its wound healing properties. Amongst the early researches Boileau P, Buzas A. et.al in 1949 published an article on the effect of CA derivatives in leprosy. [24] Study on the wound healing properties of CA continued throughout the next decade. In 1957, Thiers H *et al.* and in 1958, Boely C *et al.* found that the plant is effective in the treatment of skin ulcer and leg ulcer respectively. [25 26] Since then different researches have shown its beneficial effects on wound healing.

In vitro Studies with CA

Coldren *et al.* (2003) studied the effect of CA triterpenoids on gene expression in human fibroblast cells. The Titrated Extract of CA (TECA) was found to modulate the expression of 82 genes out of the total 1053 genes studied. CA regulates the expression of genes involved in angiogenesis, remodeling of extracellular matrix (ECM) and a variety of growth factor genes. Around twelve fold increase in the expression of Tumor Necrosis Factor Alpha –Induced Protein 6 (TNFAIP-6), a secreted hyaladherin was observed which has a central role in ECM remodeling and possesses anti-inflammatory properties. [27]

Asiaticoside present in CA affects the proliferation of human skin dermal fibroblasts and increases migration rates and enhances attachment of skin cells. [28] Asiaticoside (30 µg/mL) can upregulate the genes involved in cell proliferation, cell-cycle progression and ECM synthesis in human dermal fibroblasts. The levels of Type-I and Type-III procollagen messenger ribonucleic acid (mRNA) and protein are also increased. [29, 30] Asiaticoside increased the synthesis of Type-I collagen by activating Transforming Growth Factor Beta Receptor I Kinase (TbetaRI Kinase)-independent Smad pathway. [31] Hashim *et al.* (2011) found that ethanolic extract of CA can increase collagen synthesis in a dose dependent manner. At a dose of 50 mg/ml CA extract enhanced collagen production by three fold as compared to the control. The viability of cells was decreased at higher concentration. [32] Keloidal scars are a type of raised scar formed due to pathological wound healing. They are characterized by hyperproliferation of keloid fibroblasts, excess synthesis of extracellular matrix, abnormal cytokine and growth factor activities. Tang *et al.* (2011) studied the effect of Asiaticoside on Keloidal scars. Asiaticoside reduced proliferation and inhibited expression of Type-I and Type-III collagen and mRNAs in Keloidal fibroblasts. The expression of both Transforming Growth Factor Beta Receptor I and II (TGF-βRI and TGF-βRII) were also decreased at the transcriptional and translational level. The expression of Smad7 protein and mRNA were elevated whereas the expression of Smad2, Smad3, Smad4, phosphorylated Smad2 and Smad3 were not influenced by Asiaticoside. This shows the dual action of CA on wound healing and prevention of scar formation. [33] Aqueous extract of CA at low concentration (62.5 ppm) promoted corneal epithelial wound healing whereas at higher concentration (1000 ppm) it showed anti-proliferative effect. [34] CA is also found to promote periodontal wound healing [35].

In vivo studies with CA

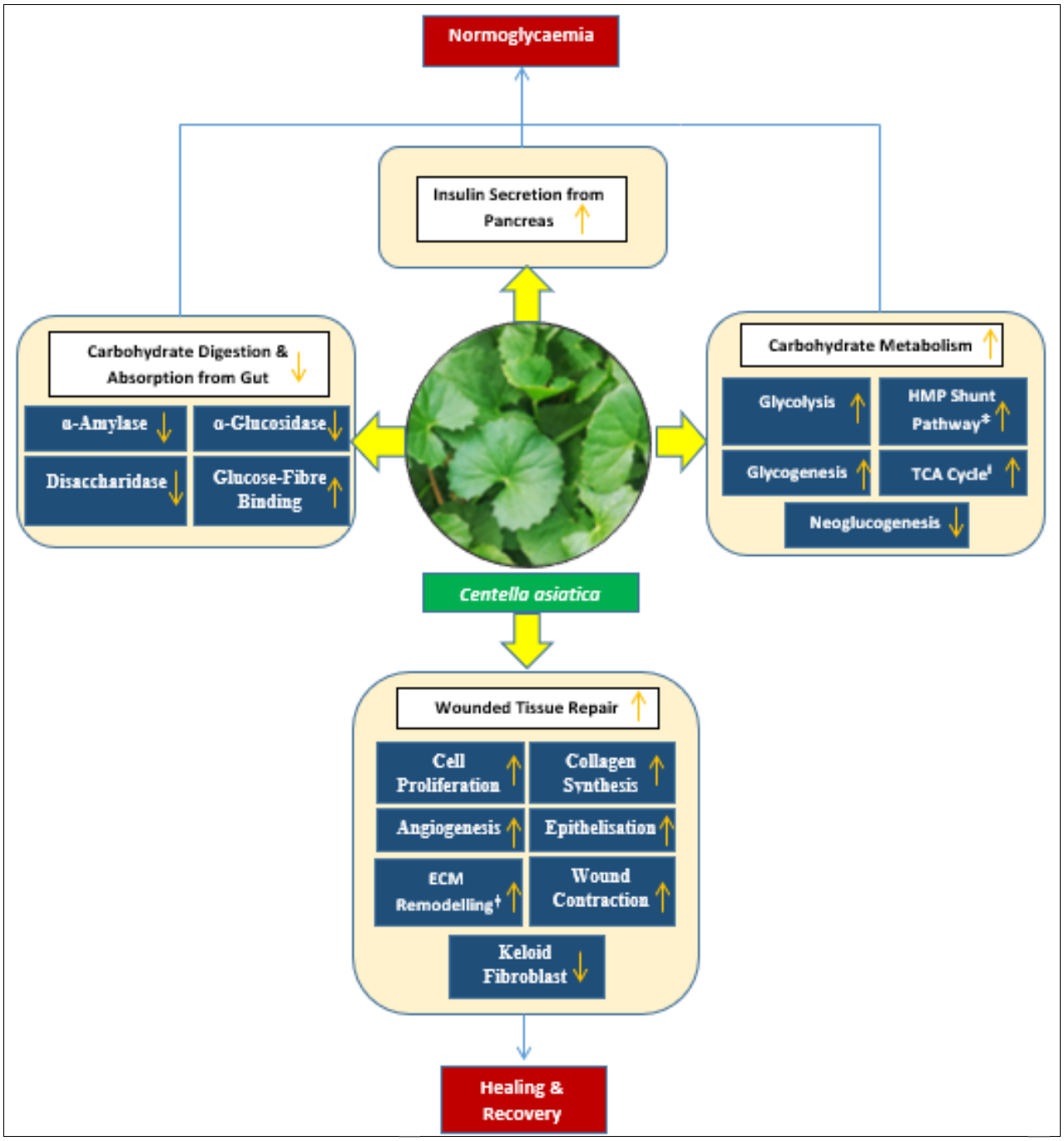
Shetty *et al.* (2006) found that ethanolic extract of CA is able to promote wound healing in both normal and dexamethasone suppressed wound. Incision, excision and dead space wound models of Wistar albino rats were studied. CA significantly enhanced the strength of wound breaking in incision wound model, the rate of wound contraction and epithelization compared to the control wounds. There was also an increase in the weights of wet and dry granulation tissue, breaking strength of granulation tissue and hydroxyproline content in dead space wound model. [36] Asiaticoside application at low doses (10(-8) to 10(-12) % (w/w)) promoted burn wound repair. The mechanism may be due to the promotion of angiogenesis as a result of the enhancement of Vascular Endothelial Growth Factor (VEGF) production caused by an increase in Monocyte Chemoattractant Protein-1 (MCP-1) expression in keratinocytes and increased expression of Interleukin-1beta in macrophages induced cooperatively by Asiaticoside and MCP-1. [37] Asiaticoside and madecassoside promoted collagen synthesis, cell growth and proliferation, induced vasodialation and reduced wound oxidative stress in male rats with burn injury. [38] Hydrogel incorporated with Asiaticoside rich fraction of CA increased incision wound healing in rabbits. The rate was 15% higher than commercial cream and >40% higher than untreated wounds. [39] Sawatdee *et al.* (2016) found that a topical spray containing CA extract complexed with hydroxypropyl-b-cyclodextrin could efficiently heal excision wound after 14 days. [40]

Clinical Studies with CA

Paocharoen *et al.* (2010) conducted a prospective randomized controlled trial (RCT) with diabetic wound patients. The intervention group received CA extract capsules (two capsules after meal thrice a day, each capsule containing 50 mg of extracted Asiaticoside) and the control group received placebo. The contraction of wound was better in the intervention group as compared to the placebo group. The formation of scar tissue was also suppressed. The authors concluded that CA extract capsules can effectively promote diabetic wound healing with no demonstrable side effect. [41] Saeidinia *et al.* (2017) evaluated the impact of a topical ointment prepared from CA extract (Centiderm) on burn wound healing. The researchers conducted an RCT where the intervention group was treated with Centiderm and control group was treated with silver sulfadiazine 1% cream (routine treatment). The wounds were treated twice a day. There was a significant improvement in all the subjective and objective signs, re-epithelialization and complete wound healing in the intervention group as compared to the control group. No infection was observed in the intervention group. [42] CA may also be beneficial for the treatment of chronic anal fissure. [43]

Discussion

The above mentioned evidences suggest a very important role of CA in the treatment of DM and wound healing. The overall mechanism is summarized in Figure 1.



Foot Note: *Thankuni* (*Centella asiatica*) increases (↑) insulin secretion, carbohydrate metabolism, wound tissue repair and decreases (↓) carbohydrate digestion and absorption leading to normoglycemia and wound healing. *Hexose Monophosphate Shunt Pathway, †Tri Carboxylic Acid Cycle, ǂ Extra Cellular Matrix Remodelling

Fig 1: Anti-diabetic and Wound Healing Mechanism of *Thankuni* (*Centella asiatica*)

Drugs conventionally used for treating DM mainly act by stimulating insulin secretion, decreasing insulin resistance, inhibiting carbohydrate digestion, glucose absorption and reabsorption. [44] CA increases the level of circulating insulin. The AA present in CA may exert hypoglycemic effects by stimulating insulin secretion from regenerated pancreatic β-cells via inhibition of Adenosine Tri Phosphate (ATP) sensitive potassium (K+) channels similar to the sulfonylurea drugs (insulin secretagogues). Inhibition of α-Amylase, α-Glucosidase and intestinal disaccharidase by CA prevents carbohydrate breakdown in the gut. Increased glucose-fiber binding further limits glucose absorption. In DM there is an increase in glycogenolytic pathway and a decrease in liver glycogen quantity. Additionally the levels of neoglucogenic enzymes increase whereas the levels of glycolytic and hexose monophosphate shunt pathway enzymes decrease. TCA cycle is also disturbed in diabetic conditions. CA shows the ability to reverse all such parameters to near normalcy. [16, 21] CA extract may also alter intracellular cyclic Adenosine Mono Phosphate (cAMP) content which may further regulate various metabolic pathways. [45] It is also beneficial in dyslipidemia and hypertension commonly observed in diabetic patients. It may also be helpful in various complications of DM like neuropathy [46], nephropathy [47],

microangiopathy [48], macular edema [49] and memory impairment due to hippocampal dysfunction. [50]

The wound healing properties of CA may be attributed to the active triterpenes compounds (Asiatic acid, Asiaticoside, Madecassic acid, Madecassoside) present in CA. These phytochemicals promote cell proliferation, cell-cycle progression and ECM synthesis in human skin fibroblasts. They enhance angiogenesis, collagen synthesis, strength of wound breaking, wound contraction, epithelization and weight of granulation tissue. These compounds also prevent scar tissue formation. Additionally CA shows anti-inflammatory [51], antimicrobial [52] and antioxidant [53] properties which might be helpful in wound healing.

Conclusions

In the present comprehensive study the medicinal value of *Thankuni* or *Centella asiatica,* specifically on diabetes mellitus and wound healing, is summarized. The study highlights the possible mechanisms by which this herb show antidiabetic and wound healing effects. These evidences further confirm the traditional knowledge regarding this herb and its potential role in the treatment of diabetes mellitus and wound healing.

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