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Review Article

Wound healing activity of *Centella asiatica*

Manasa R[1], Santosha D U[1], Meghana H D[1], Shekhara Naik R[1], Mahesh Shivananjappa[1,*]

[1] *Dept. of Food Science and Nutrition, Yuvaraja's College (Autonomous), University of Mysore, Mysuru, Karnataka, India*

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ABSTRACT

Centella asiatica is a medicinal herb in family *Apiaceae.* Commonly known as Brahmi, Gotu kola, Ondelaga, Indian pennywort and found in swampy areas and temperate regions. It has many pharmacological properties like anticancer, anti-diabetic, immunity booster, memory enhancer, wound healing, anticancer, neuroprotective. All extracts of *Centella asiatica* facilitate the wound healing process in both incision and burn wounds by inhibiting inflammation, inducing collagen synthesis, inducing vasodilation and promoting angiogenesis. This review aimed to explore the wound healing activity, botanical description, phytochemistry and traditional uses of *Centella asiatica*.

1. Introduction

The medicinal herb *Centella asiatica*(CA), a perennial plant (urban) that grows in swampy areas of tropical and subtropical regions of India, Southeast Asia and Malaysia, as well as some temperate regions of Taiwan, China, Japan and Korea. The herb known as Gotu kola or Indian pennywort, is a medicinal plant widely used in treating infectious skin diseases and accelerating the healing of skin ulcers and wounds.[1,2]

CA (Mandukparni) is known as one of the most significant Medhya herbs described in ayurvedic treatises. Acharya Charaka has described Mandukparni in four Medhya Rasayana alongside Guruchi, Shankhpushpi, and Yashtimadhu. The raw herb, as well as its alcoholic extract, is widely used in traditional as well as modern pharmacopeia's for treating stomach and duodenal ulcers, leprosy lesions, burn wounds, keloid hypertrophic scars, and neurodegenerative processes. The clinical efficacy of CA is largely accounted for by the presence of pentacyclic ursane type triterpenoid centellosides namely madecassic acid, asiatic acid, asiaticoside, and madecassoside. Amongst these, madecassoside has strong anti-inflammatory action through enhanced secretion of collagen type III, whereas asiaticoside supports wound healing by stimulating fibroblast proliferation and synthesis of collagen type-I.[3] Wound healing is a complex process, which starts immediately after injury and consists of different phases: inflammation, proliferation, maturation, and re-epithelization are the 4 main phases. These phases are further characterized at the cellular levels as fibroblast mediated fibroplasia, vessel endothelial cell-mediated angiogenesis, epithelialization and connective tissue formation which finally result in wound contraction.[4]

1.1. Taxonomy of Centella asiatica:(CA)

1. Kingdom: Plantae
2. Order: Apiales
3. Family: Apiaceae
4. Subfamily: Mackinlayoideae
5. Genus: Centella

* *Corresponding author.*
E-mail address: mayavishiva@gmail.com (M. Shivananjappa).

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6. Species: asiatica[5]

1.2. Morphological description

Small creeping herb with a slender stem, rooting at nodes giving rise to thin, brownish grey roots of about 2.7 to 6.0 cm in length; leaves 1 from each node, orbicular-reniform, cordate, base cordate, petioles channeled with adnate stipules, flowers fascicled umbels each carrying 3/4 flowers, short-stalked; fruits cremocarp, ovoid, with laterally compressed seeds.[1]

Table 1: Morphological description.[6]

Part	Characteristics
Leaves	They are arranged in small clusters of 1 to 5. Blades are attached by a long petiole 1 to 50 cm long. A leaflet is gutter and base sheathing, papery, glabrous to pubescent or woolly Limbe wide, reniform to orbicular, base cordate and apex rounded, 1 to 7 cm long and 1.5 to 9.5 cm wide. Limbe loosely hairy or woolly on the lower surface, especially the ribs. Upper surface is Glabrous (free from hair). Leaf margin is crenate to dentate and Venation is palmate.
Flower	They are small greenish-white to dark red in colour. Corolla contains 5 petals, oval – triangular shape, red – purple in colour. 5 stamens alternate with the petals. The ovary is inferior with 2 separate carpels and each surmounted by a style and a stigma. Flowers are bisexual, may be or may not be with pedicels slender, 15 mm long. Peduncle erect, long 1.6 to 5 cm, shorter than the petioles. Involucre series of bracts beneath or around a flower or flower cluster formed from 2 to 3 bracts membranous, persistent, oval to sub circular, reaching 6 mm long and purple colored. Calyx with 5 small teeth at the top of the ovary.

1.3. Parts used: Whole plant[6]

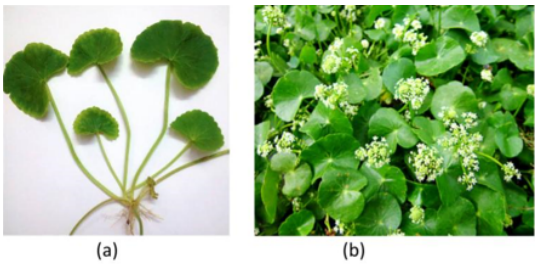


Fig. 1: (a) Leaves (b) Flower

Table 2: Vernacular names in India.[7]

Region/language	Names
Sanskrit	Manduki, Darduracchada
Assamese	Manimuni
Bengali	Jholkhuri, Thalkuri, Thankuni
English	Indian pennywort
Gujrati	Khodabrahmi, khadbhrammi
Hindi	Brahma Manduki, Brahmi
Kannada	Ondelaga, Brahmi soppu
Malayalam	Kodangal
Marathi	Karivana
Punjabi	Brahmi
Tamil	Vallarai
Telugu	Saraswati aku, vauari
dUrdu	Brahmi

Table 3: Nutritional composition of dehydrated Brahmi/100g.[8]

Nutrients	Amount
Energy (Kcal)	348
Carbohydrates(g)	68.3
Proteins (g)	13.5
Fat (g)	2.3
Iron (g)	13.8
Calcium(g)	189
Crude fibre (g)	1.6
Potassium (mg)	391
Moisture (%)	13.9
Ash (%)	1.95
Total carotene (μg)	2660

1.4. Vernacular names refer Table 2

1.5. Nutritional composition of dehydrated Brahmi/100g refer Table 3

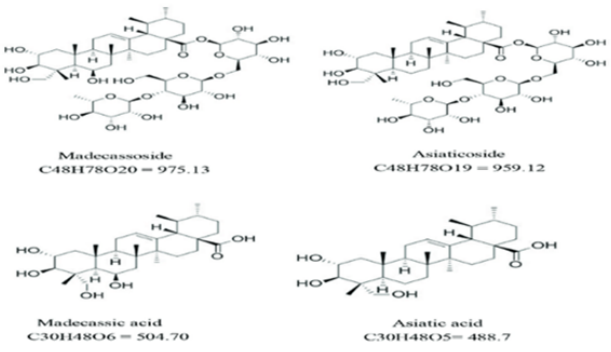
1.6. Phytochemistry

C. asiatica contains many phenolic constituents, including flavonoids, such as catechin, epicatechin, kaempferol, quercetin, and related glycosides, contains Isomeric di caffeoyl esters such as 1,3-di-caffeoylquinic acid, 1,5-di-caffeoylquinic acid, 3,4-di-caffeoylquinic acid, and 3,5-di-caffeoylquinic acid and 4,5-di-caffeoylquinic acid.[9]

The biosynthesis of flavonoids combines, shikimate pathway with the acetate pathway using p-cinnamoyl - CoA as the starter unit and three malonyl - CoA units for chain extension. Chalcone synthase forms naringenin-chalcone via a Claisen-type reaction. Flavonoids esterified to hydroxycinnamic derivatives, such as castilliferol (kaempferol-3-p-coumarate) and castillicetin (quercetin-3-caffeate) have been isolated from the aqueous methanol extracts of CA.[10]

Table 4: Chemical constituents present in different parts of centella asiatica.[3,4]

Class of compound	Chemical constituents
Phenols	1,3-dicaffeoylquinic acid,3,4-dicaffeoylquinic acid, and 3,5-dicaffeoylquinic acid and 4,5-dicaffeoylquinic acid. Di-caffeoylquinic acid catechin, epicatechin, kaempferol, quercetin, and related glycosides
1,5-dicaffeoylquinic acid	iso-chlorogenic acid A, B, or C) Irbic acid (3,5-O-di caffeoyl-4-O-malonylquinic acid)
Terpenoids	Triterpenes, asiaticoside, centelloside, madecassoside, brahmoside, brahminoside (saponin glycosides), asiaticentoic acid, centellic acid, centoic acid, madecassic acid, terminolic acid and betulic acid.
Volatile oils and fatty oils	Various terpenoids: β-caryophyllene, trans β-farnesene and germacrene D (sesquiterpenes), α-pinene and β-pinene. Fatty acids: linoleic acid, linolenic acid, lignocene, oleic acid, palmitic acid, stearic acid.
Amino acids	Alanine and serine (major components), amino butyrate, aspartate, glutamate, histidine, lysine, threonine, arginine, leucine, iso-leucine, valine, methionine, tyrosine, phenylalanine, proline, cystine, glycine.
Flavonoids (hydroxycinnamic derivatives)	Castilliferol (kaempferol-3-p-coumarate) and castillicetin (quercetin-3-caffeate)
Other components	Tannins, steroids terpenoids, alkaloids, saponins



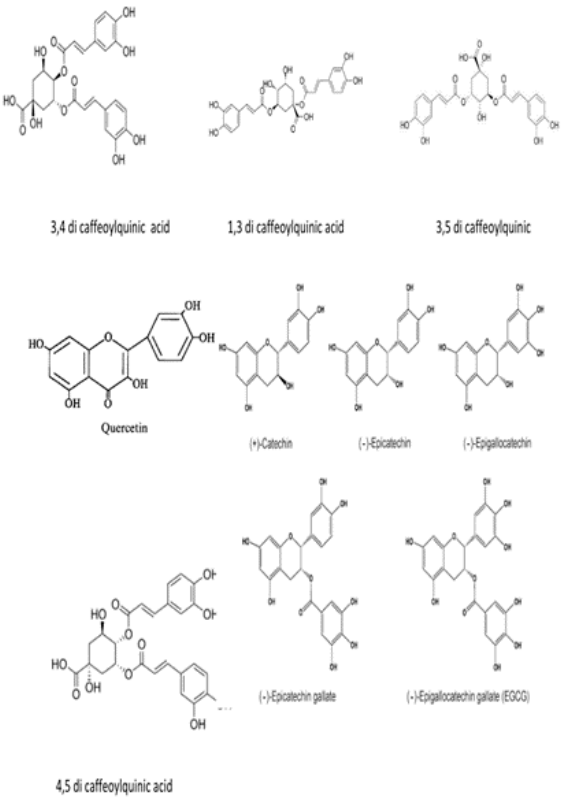


Fig. 2: Chemical constituents present in different parts of *Centella asiatica.*[11]

1.7. Pharmacological studies

Centella asiatica, commonly known as gotu kola, is an herbaceous plant belonging to the family Mackinlayaceae. It is a mild adaptogen and has been used as a medicinal herb for thousands of years in India, where it is commonly used in antiaging preparations for the skin.[12] According to Charaka, Gotu kola is a very useful medicinal plant in preventing aging. It is ranked high in the top ten herbs known for antiaging properties and this may be due to its antioxidative effects.[13,14]

The CA extracts (CAE) have been used traditionally for wound healing and the research has been increasingly supportive for these claims. A preclinical study reports that various formulations (ointment, gel and cream) of an aqueous CAE applied to open wounds resulted in increased cellular proliferation and collagen synthesis at the wound site, the CAE-treated wounds showed epithelialized faster and the rate of wound contraction will be higher when compared to the untreated wound. Healing was more prominent with the gel product. It is believed to have an effect on keratinization, which aids in thickening skin in areas of infection.[15]

1.8. Animal study

Yao et al Studied Wound-healing effect of Electrospun gelatin nanofibres containing *Centella asiatica* extract on male Sprague–Dawley rats' model. Wound was induced by using a sharp sterile scalpel, the rats treated with CAM (methanol) in EGC (electrospun gelatin) membrane 31.2 mg/ml for 14 consecutive days. This study revealed EGC membrane was excellent matrix for cell growth, increased wound recovery, increased Granulation tissue, increased numbers of capillaries in the wound areas. On 7^{th} day the amount of CA that was released from these EGC membranes was better able to promote cell proliferation.[5]

Sawatdee et al studied the topical spray containing *Centella asiatica* extract and its efficacy on excision wounds in male wistar rats. Incision was made using scalpel measuring about 200 mm, the rats were treated with Triterpenes (methanol) extract hydroxypropyl-b-cyclodextrin (HP-b-CD) complexed topical spray, ~2.5 mL in spray form for 14 consecutive days. Results in increased tensile strength in newly formed skin, increased synthesis of collagen. Acidic mucopolysaccharides inhibit the inflammatory phase that causes hypertrophic scars and keloids decreased lipid peroxide levels.[16]

Sh Ahmed et al Studied Pharmacological properties of *Centella asiatica* hydrogel in accelerating wound healing in male White Albino rabbits. Wound was induced 1cm long incision was made using a sharp scalpel Rat were treated with Asiaticoside (Ethanol extract) 24 mg of fraction, PVA (8%) PEG (5%) polyethylene glycol/ polyvinyl alcohol (PEG/PVA) hydrogel was applied for 12 days. This study showed that there was increase in antioxidant levels, wound contraction, period of epithelization, promote fibroblast proliferation and extracellular matrix (ECM) synthesis, better recovery.[17]

Bian et al studied the identification of Major Active ingredients responsible for Burn Wound Healing of *Centella asiatica* herbs on male ICR mice. Active ingredients are glycosides (asiaticoside and madecassoside) burn wound was made by Direct contact between a brass rod (65 g, 1 cm in diameter) heated to 95°C and was kept for 9 seconds to induce full-thickness burn wound on skin. group 1 asiaticoside (24 mg/kg) and group Madecassoside (24 mg/kg) for 2 weeks. In this study mice showed increased collagen type I and type III activating skin fibroblasts via TGF-β/Smad pathway and increased wound healing speed. It is noteworthy that madecassoside possess a more potent therapeutic agent.[18]

1.9. In vitro study

Biane et al.,2012 studied the identification of major active ingredients responsible for burn wound healing of *Centella asiatica* herbs. Primary human skin fibroblasts were obtained from healthy foreskin samples of patients with ablative surgery via enzymatic digestion. Madecassoside 10 μm for 24hr resulted elevated mRNA levels of collagen type I and type III in fibroblasts as well as protein levels of procollagen type I and type III as detected. This study showed madecassoside 10 μm significantly increase in TGF-β 1 and TβRII mRNA expression and increase inPhosphorylation levels of SMAD 3 in fibroblast, increase in TIMP-1 mRNA expression.[18]

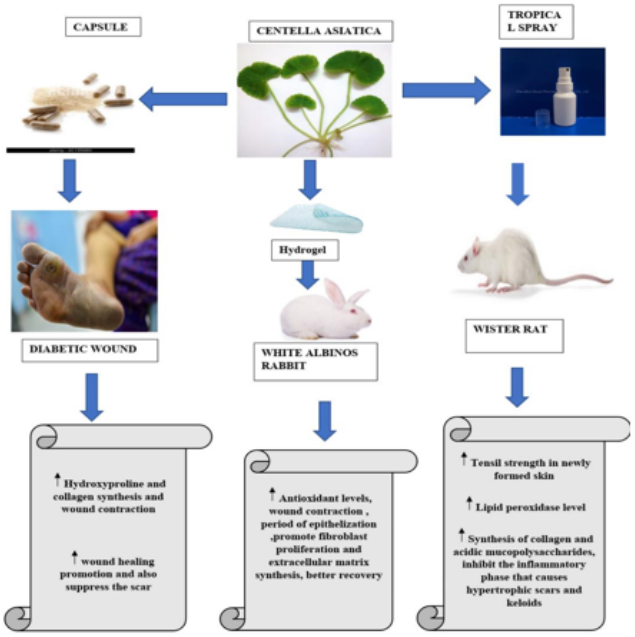


Fig. 3: Schematic representation of wound healing activity of *Centella asiatica*

1.10. Human study

Paocharoen (2010) studied the efficacy and side effects of oral *Centella asiatica* extract for wound healing promotion in diabetic wound patients. Treated with CA extract 50 mg of 2 capsules 3 times/day for 21 days. In this study they showed increased Hydroxyproline and collagen synthesis and wound contraction increased effectively in the wound healing promotion and also suppress the scar.[19]

2. Conclusion

Centella asiatica is a traditional herb commonly known as Indian penny wort acts as a barrier in restoring the moisture of the skin. It protects skin from breaking down even more, especially for sensitive skin which is red, inflamed, irritated or itchy. It helps in reducing the visible signs of skin sensitivity such as itching and burning significantly. It also helps in wound healing action.

Table 5:

Sl. no	Model	Treatment	Result	Reference
01	SD rats Scalpel incision 40 cm n=6	CA (methanol)Extract in EGC membrane 31.2 mg/ml for 21 days	Excellent matrix for cell growth, Wound recovery, Granulation tissue 30% Numbers of capillaries in the wound areas on 7^{th} day	5
02	Wistar rats, scalpel incision 200 mm^2 n=6	CA Triterpenes (methanol) extract CD complexed topical spray, 2.5 mL for 14 days	Tensile strength in newly formed skin Synthesis of collagen and acidic mucopolysaccharides, inhibit the inflammatory phase that causes hypertrophic scars and keloids	16
03	White Albino rabbits Scalpel incision 1 cm n=6	Asiaticoside (Ethanol) extract 24 mg of fraction, hydrogel for 12 days	Lipid peroxide levels Antioxidant levels, wound contraction Epithelization	17
04	Albino mice Burn wound Brass rod (65 g, 1 cm in diameter,9 sec) n=24	Madecassoside (24 mg/kg) distilled H2O oral for 14 days	Promote fibroblast proliferation, ECM synthesis by 20%, better recovery Collagen type I and type III activating skin fibroblasts via TGF-β/Smad pathway Wound healing speed	18

[SD=Sprague Dawley rat, CAME=*Centella asiatica* methanol extract, EGC = electrospun gelatin nanofibers, CD Complex =conventional drug complex topical spray, ICR MICE=institute of cancer research mice, TGF-β/S MAD=transformation growth factor beta mother against decapentaplegic pathway].

Table 6: Wound healing activity of *Centella asiatica* on invitro

Sl no	Model	Treatment	Result	Reference
01	Primary human skin fibroblasts	Madecassoside,10 μm for 24hrS	TGF-β 1 and TβRII mRNA levels of collagen type I and type III in fibroblasts Protein levels of procollagen type I and type III as detected TIMP-1, mRNA expression Phosphorylation levels of SMAD 3	18

[TGF -β_1 transformation growth factor beta 1, MRNA= messenger RNA, SMAD=mothers against decapentaplegic, TIMP=tissue inhibitor of metalloproteinase].

Table 7: Wound healing activity of *Centella asiatica* on humans

Sl no	Model	Treatment	Result	Reference
01	Diabetic wound patients n=84	CA Asiaticoside extract 50mg of 2 capsule 3times/d for 21 days	Hydroxyproline and collagen synthesis wound contraction wound healing promotion and also suppress the scar	19

In the above Study's, shows the effect of *Centella asiatica* plant on wound healing, like wound contraction, tissue growth, inflammation, proliferation, maturation, and re-epithelization and other activity, hence used in ayurvedic medicines.

3. Source of Funding

None.

4. Conflict of Interest

None.

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Author biography

Manasa R, Research Scholar

Santosha D U, Consultant

Meghana H D, Consultant

Shekhara Naik R, Professor and Head

Mahesh Shivananjappa, Assistant Professor

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