

Centella asiatica: Unveiling Its Role in Wound Healing and Tissue Regeneration

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Abstract: Regeneration and tissue repair processes consist of a sequence of molecular and cellular events which occur after the onset of a tissue lesion in order to restore the damaged tissue. The efficacy of *Centella asiatica* for incision and burn wounds are not fully understood. Here, we report the wound healing activities of sequential hexane, ethyl acetate, methanol, and water extracts of *Centella asiatica* in incision and partial-thickness burn wound healing. There is a higher demand for nutrients which needs to be met. This is to reduce the risk of delay in wound healing which could lead to chronic wound. This is a systematic review of the effect of *Centella asiatica* on wound healing. *Centella asiatica* is a reputed medicinal plant used in the treatment of various skin diseases in the Indian system of medicine. The aerial parts and roots are used for medicinal purpose, and its chemical constituents have wide therapeutic applications in areas of antimicrobial, anti-inflammatory, anticancer, neuroprotective, antioxidant, and wound healing activities. Triterpenoid, saponins, the primary constituents of *Centella asiatica* are mainly believed to be responsible for its wide therapeutic actions. It is widely distributed throughout tropical and subtropical regions of World. The use of *Centella* in food and beverages has increased over the years basically due to its beneficial functional properties. The therapeutic substances in *C. asiatica* are saponin-containing triterpene acids and their sugar esters, of which asiatic acid, madecassic acid and asiaticosides are considered to be the most important.

Keywords: Wound, Morphology, Pharmacology action, Wound healing, Anti fungal activity, Anti inflammatory activity.

INTRODUCTION

1.1 Wound

A wound is an injury to the body, often involving a break in the skin, and can take various forms such as burns, lacerations, abrasions, contusions, and incised wounds. Healing from a wound occurs in four overlapping stages that begin right after the injury and can extend over several years. This healing process is nonlinear and may fluctuate through the stages due to external and internal factors like growth factors and cytokines. (1) Collagen is essential for repairing tissue defects and restoring anatomical structure and function after an injury. *Centella asiatica*, applied topically, is known to enhance wound healing, though research on its mechanisms and effectiveness is still developing. Following an injury, tissue regeneration and repair processes begin. (2) These processes are triggered by trauma or specific clinical conditions that disrupt the normal physical integrity of tissues, leading to the formation of lesions. Such lesions can be caused by various internal or external stimuli, including physical, chemical, electrical, or thermal factors, and may damage specific organelles or the cells themselves. (3) The wound healing process relies on key activities such as angiogenesis, collagen synthesis, epithelialization, and wound contraction. Various factors, including pharmacological, chemical, and physical elements, can aid in this process. Research has confirmed that *Centella asiatica* has pharmacological effects that support wound healing. (4)

CENTELLA ASIATICA

Centella asiatica is a herbaceous perennial plant that belongs to the Apiaceae family, also called Umbelliferae. It is also known by other names, such as Gotu Kola, Bua-bok, Tiger grass, or Indian Pennywort. (5) In parts of China, Southeast Asia, India, Sri Lanka, Oceania, and Africa, *Centella asiatica* has long been consumed as a vegetable. It is widely used in Southeast Asia to cure a wide range of illnesses, such as rheumatism, inflammation, syphilis, mental sickness, epilepsy, hysteria, diarrhea, and skin problems. Gotu Kola is used in Indian medicine to heal nerve illnesses, skin conditions, and improve memory. At elevations of up to 1800 meters, *Centella asiatica* flourishes in damp conditions. It is frequently found in marshy areas in a wide range of tropical and subtropical nations, including some areas of India. (6) This paper traces the historical development of *Centella asiatica*'s medicinal usage and provides a thorough summary of our current knowledge of the plant's

pharmacology, botany, and clinical-therapeutic uses. *Centella asiatica* is a perennial herbaceous creeper with fan-shaped leaves that can reach a height of 30 cm. For generations, it has been a part of traditional Asian medicine. Triterpene saponins, such as asiaticoside, madecassoside, madecassic acid, and sapogenin asiatic acid, are the main components of *Centella asiatica*. (7) Because *Centella asiatica* has so many health benefits—such as being an antioxidant, an anti-inflammatory, a wound healer, and a memory enhancer—its usage in food and drink has increased dramatically over time. Recently, there has been a lot of interest in *Centella*'s potential as a natural antioxidant, especially one derived from plants, and its function in preventing age-related alterations in the antioxidant defense system of the brain. *Centella asiatica* is an important medicinal plant in the world's medicinal plant commerce, according to reports from the Export and Import Bank of India. However, the wild population of this plant has drastically decreased as a result of extensive and uncontrolled extraction, insufficient cultivation, and insufficient efforts to replenish. Consequently, *Centella asiatica* is now recognized as an endangered species and has been designated as such by the International Union for Conservation of Nature and Natural Resources (IUCN). (8) It is also suggested for the treatment of venous insufficiency and as an antipyretic, diuretic, rheumatic, antibacterial, and antiviral medication. It is also utilized as an anti-cancer drug, to reduce anxiety, and to enhance cognition. Historically, *Centella asiatica* was also used to treat bug bites, mild irritation, leprosy, hysteria, and epilepsy. The existing list of this plant's health advantages is out of date, especially in light of the most recent studies, even though it has been well studied. Furthermore, it's uncertain what other toxicities could arise from consuming it. As a result, the purpose of this review is to evaluate the toxicity levels of *Centella asiatica* and to update our knowledge of its health advantages. (9) Inflammation is characterized by redness, swelling, heat, and pain. Histamine is a substance that is released by mast cells in response to damage to human tissues. Heat and redness are brought on by histamine's increased blood flow to the injured location. Furthermore, capillaries start to leak, which causes edema. (10)



TOXONOMY

The taxonomic classification of *Centella asiatica* is as follows:

Kingdom: Plantae

Division: Angiosperms

Class: Eudicots

Order: Apiales

Family: Apiaceae (Umbelliferae)

Genus: *Centella*

Species: *Centella asiatica*

Morphology

Centella asiatica is a perennial creeping herb that grows slowly and has a mild perfume. It may grow up to 15 cm tall thanks to its stolons. The stem roots at the nodes and is striated and smooth. In places like paddy fields and riverbanks that are shaded, swampy, damp, and moist, *Centella asiatica* grows and creates a thick carpet of greenery. Compared to clayey soil, sandy loam soil, which contains 60% sand, is better for its regeneration. There are one to three long-petioled leaves per stem node, with dimensions of 2 to 6 cm in length and 1.5 to 5 cm in breadth. The leaves have a sheathing leaf base, a smooth surface on both sides, and a crenate border (see to Fig. A).(11) The blooms bloom from April to June and are grouped in fascicled umbels, with three to four white, purple, or pink flowers in each.. Throughout the growth season, fruits with a highly thickened pericarp and an oblong, globular form, typically about 2 inches in length, are produced. An embryo that is pendulous and laterally compressed is present in the seeds. Typically, *Centella asiatica* may be found up to 600 meters above sea level in India's tropical and subtropical climates. Higher altitudes, such as 1200 meters at Mount Abu, Rajasthan, and 1550 meters in Sikkim, have also seen it, though.(12) The aforementioned plant is indigenous to many regions of Southeast Asia, India, Sri Lanka, China, Madagascar, South Africa, the Western South Sea Islands, the Southeast United States, Mexico, Venezuela, Colombia, and Eastern South America.(13)

Table 1: Vernacular names in different regions of India and Abroad.

In India:			
Region/ Language	Vernacular Name	Region/ Language	Vernacular Name
Hindi	Bemgsag, Brahma-Manduki, Gotukola, Khulakhudi, Mandookaparni	Sanskrit	Bhekaparni, Bheki, Brahmamanduki, Darduchhada, Divya, Mahaushadhi, Mandukaparnika, Manduki, Mutthil, Supriya, Tvasthi
Malayalam	Kodagam, Kodangal, Kutakm, Kutannal, Muthal, Muttil, Muyalchevi	Kanarese	Brahmisoppu, Urage, Vandelaga-illikiwigidda, Vondelaga [
Telugu	Bekaparnamu, Bokkudu, Saraswataku, Mandukbrahmami, Saraswati plant	Gujrati	Barmi, Moti Brahmi
Marathi	Karinga, Karivana	Tamil	Babassa, Vallarai
Tripura	Thankuni, Thunimankuni	Bengal	Thankuni, Tholkuri
Assam	Manimuni	Deccan	Vallarai
Bihar	Chokiora	Meghalaya	Bat-maina
Oriya	Thalkudi	Snhalese	Hingotukola
Urdu	Brahmi		

Chemical constituents

The plant has long been utilized in traditional medicine to treat various ailments. Its therapeutic properties have been linked to specific chemical compounds identified in it. Asiatic acid, asiaticoside, and madecassoside are the primary constituents responsible for its pharmacological effects, in addition to its richness in flavonoids and terpenoids.(14) *Centella's* triterpenes consist of a variety of compounds, including asiatic acid, madecassic acid, asiaticoside, madecassoside, brahmoside, brahmic acid, brahminoside, thankinise, isothankuniside, centelloside, madasiatic acid, centic acid, and cenellic acid. Saponins may constitute 1% to 8% of all constituents in *Centella asiatica*. Gas chromatography-mass spectrometry (GC-MS) analysis revealed that p-cymene (44%) and other volatile compounds are present in significant amounts in the essential oil of *Centella asiatica*.(16)

Centella asiatica is reported to have following types of chemical compounds:

- Triterpenoids
- Volatiles and fatty acids
- Alkaloids
- Glycosides
- Flavanoids
- Others- Vitamin B, C, G and some amino acids etc.
- Triterpenoids : asiatic acid, asiaticoside, madecassic acid, madecassoside, terminolic, centic, centellic, centoic acid, indocentoic acid, isobrahmic, brahmic, betulic, and madasiatic acid. The compound has been identified as 2,6-hydroxy, 23-hydroxy-methyl ursolic acid. Asiaticoside and madecassoside are predominant in the leaves, with lower concentrations found in the roots.(17)
- Volatiles and fatty acids: The fatty oil consists of glycerides of palmitic, stearic, lignoceric, oleic, linoleic and linolenic acids.
- Alkaloids: hydrocotylin.
- Glycosides : "Asiaticoside A, asiaticoside B, madecassoside, centelloside, brahmoside, brahminoside, thankuniside, glycoside D, and glycoside E.

- Flavanoids: "Flavonoids such as 3-glucosylquercetin, 3-glucosylkaempferol, and 7-glucosylkaempferol have been isolated from the leaves. The plant is also reported to contain tannins, sugars, inorganic acids, and resin, along with amino acids like aspartic acid, glycine, glutamic acid, α -alanine, and phenylalanine. The total ash content includes chloride, sulfate, phosphate, iron, calcium, magnesium, sodium, and potassium. Additionally, the leaves are rich in vitamins such as vitamin B, vitamin C, and vitamin G(18)



Fig. 1: Pharmacological activities of *Centella asiatica*

WOUND HEALING

The extract of *Centella asiatica* significantly enhanced wound closure in the incision model compared to controls. The wound contraction rate was markedly improved in comparison to the control group and wounds treated with the extract epithelialized more quickly.(19)The wound healing properties of *Centella asiatica* have been harnessed in various forms, including topical ointments, creams, and extracts. Clinical studies have shown its efficacy in treating a range of wound types, including surgical wounds, ulcers, and burns. Additionally, it has been found to reduce scar formation, making it a popular ingredient in post-surgical care and cosmetic formulations. The therapeutic potential of *Centella asiatica* in wound care is attributed to its rich content of bioactive compounds such as triterpenoids (asiaticoside, madecassoside), flavonoids, and polyphenols, which collectively contribute to its efficacy in promoting skin repair and regeneration.(20)

ANTI-DEPRESSANT PROPERTY

Centella asiatica, also known as Gotu Kola, has been traditionally used in Ayurvedic and Chinese medicine not only for its wound healing properties but also for its potential benefits in mental health, particularly as an antidepressant. The herb's neuroprotective and cognitive-enhancing effects have garnered significant attention in recent years, with several studies investigating its role in alleviating symptoms of depression and

anxiety. Compared to diazepam *C. asiatica* possesses an anxiolytic effect but has no effect on behavioral despair. (21) Total triterpenes and imipramine from *C. asiatica* were evaluated for antidepressant activity using forced swimming test, the result showed a reduction in stillness duration and regulated amino acid levels. In another study, decrease in corticosterone level in serum and enhanced 5-HT, NE, DA and their metabolites 5-HIAA and MHPG in rat brain were observed. (22)

ANTIDIABETIC ACTIVITY

The antidiabetic properties of *Centella asiatica* leaf extract were assessed in alloxan-induced diabetic rats. Following the administration of the extract at concentrations of 250, 500, and 1000 mg/kg, a reduction in blood glucose levels was observed after 3 hours. (23) The reductions were 32.6%, 38.8%, and 29.9%, respectively, demonstrating a dose-dependent effect on glucose regulation. *Centella asiatica* extract and rutin exhibited lower α -amylase inhibitory activities compared to acarbose, a standard antidiabetic drug. However, the extract demonstrated a dose-dependent reduction in blood glucose levels. At doses of 50, 100, 200, and 400 mg/kg body weight, blood glucose levels were reduced by 29.4%, 32.8%, 33.6%, and 35.7%, respectively. Animal studies and in vitro models suggest that *Centella asiatica* extracts can lower fasting blood glucose levels. (24) This effect is often linked to the plant's ability to modulate enzymes involved in glucose metabolism, such as glucose-6-phosphatase and hexokinase. By inhibiting glucose production in the liver and promoting glucose utilization in tissues, *Centella asiatica* contributes to overall glycemic control. Although clinical trials in humans are limited, preliminary studies suggest that *Centella asiatica* may help improve glycemic control and mitigate diabetes-related complications. (25)

COGNITIVE FUNCTION

The water extract of *Centella asiatica* has been shown to promote synaptic differentiation and dendritic arborization, particularly in response to A β , contributing to cognitive improvement. In another study, supplementation with Gotu kola extract over several weeks demonstrated effectiveness in treating cognitive impairment following a stroke. (26) A study demonstrated the cognitive-enhancing and antioxidant properties of *Centella asiatica* in normal rats. The effects of aqueous *Centella asiatica* extracts (100, 200, and 300 mg/kg for 21 days) were evaluated in rats with intracerebroventricular (i.c.v.) streptozotocin (STZ)-induced cognitive impairment and oxidative stress. Rats treated with *Centella asiatica* showed a dose-dependent improvement in cognitive behavior, as seen in passive avoidance and elevated plus-maze tests. Significant reductions in malondialdehyde (MDA) levels, along with increases in glutathione and catalase levels, were observed in rats treated with 200 and 300 mg/kg of the extract. (27) Given that oxidative stress and impaired endogenous antioxidant mechanisms are key factors in Alzheimer's disease (AD) and cognitive decline in the elderly, this model of i.c.v. STZ-induced impairment in rats has been linked to sporadic AD in humans, with cognitive impairment attributed to free radical generation. (28)

HEPATOPROTECTIVE

The hepatoprotective activity of *Centella asiatica* extract was evaluated against CCl₄-induced liver injury, with the extract demonstrating significant protective effects, likely due to the presence of asiaticoside (14.5%). The functional groups of asiatic acid were modified at positions C2, C3, C23, and C28, and the compound exhibited hepatoprotective effects against GalN-induced hepatotoxicity, offering 66.4% protection at a concentration of 50 μ M, and moderate protection against CCl₄-induced hepatotoxicity with 20.7% protection at the same concentration. Asiatic acid helps prevent liver injury by initiating Smad7-dependent inhibition of TGF- β /Smad-mediated fibrogenesis. Traditionally used plants for treating liver dysfunction may thus serve as valuable sources of hepatoprotective compounds for the development of new pharmaceutical agents. (29) Among its many therapeutic benefits, the hepatoprotective properties of *Centella asiatica* have garnered significant attention. The liver, being a vital organ involved in detoxification and metabolism, is susceptible to damage from toxins, drugs, and oxidative stress. Various studies have highlighted the ability of *Centella asiatica* to protect the liver from injury, particularly due to its rich content of bioactive compounds such as asiaticoside, asiatic acid, and madecassoside. (30)

ANTICANCER ACTIVITY

The aqueous extract of *Centella asiatica* demonstrated inhibitory activity against human breast cancer (MDA MB-231), mouse melanoma (B16F1), and rat glioma cell lines, with IC₅₀ values of 698.0, 648.0, and 1000.0 μ g/mL, respectively. (31) Additionally, the methanolic extract of *C. asiatica* showed an inhibitory effect on MCF-7 breast cancer cell lines, inducing apoptosis as evidenced by nuclear condensation, increased annexin staining, mitochondrial membrane potential loss, and DNA breaks detected through TUNEL assay. The juice of *C. asiatica* was tested on the human HepG2 cell line using the MTT assay, exhibiting dose-dependent cytotoxic effects. At concentrations above 0.1%, significant DNA damage and apoptotic cell death were observed in HepG2 cells. This antiproliferative effect is largely attributed to the presence of triterpenoids, which interfere with the growth and survival of cancer cells. By inhibiting the cell cycle, *C. asiatica* prevents the uncontrolled division and growth of tumor cells, ultimately reducing tumor progression. Studies have shown that both aqueous and methanolic

extracts of *C. (32)asiatica* can trigger apoptosis in breast cancer (MCF-7) and other cancer cell lines. Apoptosis induction is evidenced by nuclear condensation, increased annexin V staining, mitochondrial membrane potential loss, and the activation of caspases. DNA fragmentation, as observed through TUNEL assays, confirms that *C. asiatica* promotes apoptotic cell death in cancer cells.(33)

ANTIBACTERIAL ACTIVITY

Centella asiatica exhibits antibacterial activity primarily by disrupting bacterial cell membranes. Its bioactive compounds, particularly asiatic acid and madecassic acid, can penetrate bacterial membranes, leading to increased permeability and cell lysis.(34) This membrane-disruptive effect weakens the structural integrity of bacterial cells, making them more vulnerable to other antibacterial agents or the host's immune system. anti-biofilm activity, preventing the formation and persistence of biofilms, which are protective layers that bacteria form to shield themselves from antibiotics and the immune system. This ability to inhibit biofilm formation is particularly significant in treating chronic bacterial infections, where biofilms contribute to antibiotic resistance. Studies have demonstrated that *Centella asiatica* can reduce biofilm formation in bacteria such as *Staphylococcus aureus* and *Escherichia coli*, making it a promising agent for combating bacterial persistence in infections. its wound-healing properties, and its antibacterial effects play a key role in preventing infection in wound sites.(35) In studies where *C. asiatica* extracts were applied to wounds, not only did the plant enhance collagen synthesis and tissue regeneration, but it also significantly reduced bacterial colonization at the wound site. This dual action makes *Centella asiatica* a valuable agent for treating wounds and ulcers that are prone to bacterial infections.(36)

ANTIFUNGAL ACTIVITY

The antifungal properties of *Centella asiatica* are largely attributed to its ability to disrupt fungal cell membranes. Its triterpenoid compounds, particularly asiatic acid and madecassic acid, interact with fungal cell walls and membranes, compromising their integrity.(37) This leads to increased membrane permeability, resulting in the leakage of essential cellular contents and eventual fungal cell death. Studies have shown that extracts of *Centella asiatica* can inhibit the growth of various fungal species, including *Candida albicans*, *Aspergillus niger*, and *Trichophyton rubrum*. These effects are dose-dependent, with higher concentrations of the plant extract exerting greater inhibitory activity. Fungal biofilms are complex structures that protect the fungal cells from antifungal agents, making infections more difficult to treat. By inhibiting biofilm formation, *C. asiatica* enhances the susceptibility of fungi to treatment and reduces the risk of persistent or chronic fungal infections.(38)

ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory methodologies are commonly employed in experimental oncology to assess the inflammation-modulating potential of both natural compounds, such as betulinic acid, α -amyrin acetate, lupeol acetate, oleanolic acid, and ursolic acid, and synthetic agents. Terpenoids, which are primary constituents of secondary metabolites produced by plants, play a significant role in stress response and defense mechanisms. Plants with medicinal properties, including those rich in compounds like ceramides and various forms of terpenoids, are known for their therapeutic potential. Pentacyclic triterpenoids and saponins, collectively referred to as centelloids, are particularly important, with triterpenoid saponins believed to be the primary contributors to the therapeutic effects of these plants.(39) anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). These cytokines play a central role in initiating and sustaining inflammatory responses. Bioactive compounds in *C. asiatica*, such as asiaticoside and madecassoside, have been shown to suppress the activation of nuclear factor-kappa B (NF- κ B), a key transcription factor involved in the expression of pro-inflammatory genes. The results indicated that the methanolic extract exhibited significant anti-inflammatory activity, with the most pronounced effect observed at 3 hours post-injection, particularly at a dose of 200 mg/kg. This effect was slightly less than that of indomethacin.(40)

Conclusion:

In conclusion, *Centella asiatica*, often hailed as a powerhouse in traditional medicine, has demonstrated remarkable potential in the realms of wound healing and tissue regeneration. Its active compounds, such as asiaticoside, madecassoside, and asiatic acid, play pivotal roles in enhancing collagen synthesis, reducing inflammation, and accelerating cellular repair processes. Emerging research underscores its efficacy not only in promoting faster wound closure but also in improving the quality of healed tissue. As we continue to explore and validate its benefits through rigorous scientific studies, *Centella asiatica* could increasingly become a cornerstone in modern therapeutic practices, bridging the gap between traditional remedies and contemporary medical advancements. Its promising profile warrants further investigation and could lead to innovative treatments that harness its natural healing prowess.

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