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*Review*

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# *Centella asiatica* - A review of its medicinal uses and pharmacological effects

**D. Arora[1], M. Kumar*[1], S. D. Dubey[2]**

1. Department of Pharmacology, Universal College of Medical Sciences, Bhairahawa, Nepal
2. Department of Dravyaguna, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

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**Abstract**

*Centella asiatica*, a medicinal herb widely distributed throughout the world is popular as a traditional medicine. In Ayurveda, it is used either alone or as an important ingredient of several formulations for the management of CNS, skin and gastrointestinal diseases. Several of its traditional uses have been scientifically validated and some of the active principles have also been reported. This review focuses on the details of its medicinal uses with emphasis on the pharmacological actions.

**Key words:** *Centella asiatica*, phytotherapy.

## 1. Introduction

*Centella asiatica* (L) urban, synonym *Hydrocotyle asiatica,* belongs to the family Apiaceae (Umbelliferae). This herb is found almost all over the world, particularly during rainy season and in damp and marshy areas. It is a popular medicinal plant in several traditional systems of medicine. In Ayurveda, an Indian system of medicine, this is an important ingredient of several compound formulations used in the management of central nervous system, skin and gastrointestinal disorders.

It is also used alone and has been considered by Vagbhatt as the best herb for improving memory and intellect. It belongs to the group of drugs known as medhya rasayanas (psychotropic drugs) and is also known as Brahmi. The literal, meaning of the term, Brahmi is one which promotes the intellect and that is why many herbs with similar effects are known as Brahmi. This has led to the popular controversy associated with this herb, as presently two herbs, *viz. Centella asiatica* and *Bacopa monnieri,* are used by the same name of Brahmi in different parts of India.

To avoid the confusion, it has been suggested to refer this plant by its other name mandukaparni, a synonym indicating towards its peculiar leaves

* Corresponding author

[1]. In English this is known as waternavel, waterpennywort and Indianpennywort.

## 2. Botanical description

*Centella asiatica* (CA) is a slender trailing herb, rooting at the nodes. It has long, reddish, prostate stem emerging from the leaf axils of a vertical root stock. Leaves are orbicular, reniform, entire, crenate, glaborous, 1.3-7 cm in diameter. Flowers are sessile, white or reddish, covered by bracts and 3-6 flowers are arranged in an umbel. Fruits are small, compressed, 8 mm long, mericarps are curved, rounded at the top, broad and 7-9 ridged. Seeds are compressed laterally. This has a characteristic odour, greyish green colour and bittersweet taste.

## 3. Habitat

The plant is indigenous to the warmer regions of both the hemispheres, including Asia, Africa, Australia, southern United States of America, Central America and South America. It is specially abundant in the swampy areas of India, upto an altitude of approximately 700 m. It is abundantly found during rainy season.

## 4. Therapeutic uses in traditional systems of medicine

In Ayurveda, it is a popular rasayana drug and is used as medhya rasayana in the CNS disorders like epilepsy, schizophrenia and cognitive dysfunction. It also finds use in renal stones, leprosy and skin diseases, anorexia and asthma. In other traditional systems, it has been additionally used in the management of diarrhoea, cholera, measles, jaundice, leukorrhoea, haematemesis, hepatitis, urethritis, toothache, syphilis, smallpox, neuralgia, rheumatism, toothache and varices; and as an antipyretic, analgesic and antiinflammatory. Poultices have been used to treat contusions, closed fractures, sprains and furunculosis [2].

## 5. Chemical constitutents

The major principles in the plant are the triterpenes, asiatic acid and madecassic acid and their derived triterpene ester glycosides, asiaticoside and madecassoside [3]. The whole plant on extraction with diethyl ether has yielded β-pinene, α-terpinene, bornyl acetate, α-copaene, β-elemene, β-caryophyllene, trans-β-farnesene, germacrene-D and bicycloelemene through GC-MS analysis [4].

From the underground parts of CA, many polyacetylenic compounds were isolated, the major compound being 8-acetoxyfalcarinol [5]. The amino acid study of the plant indicated that in the leaf, petiole and stolon, the percentage of glutamine and serine is more than other amino acids. The roots are rich in amino acids, specially aspartic, glutamic, serine, threonine, alanine, lysine and histidine [6].

## 6. Pharmacokinetics

Grimaldi has worked out the pharmacokinetics of asiatic acid after oral administration of total triterpenic fraction of CA [7]. It has been shown that repeated oral administration of total triterpenic fraction daily for 7 days produces a significantly higher $t_{½\beta}$ and $AUC_{0\text{-}24}$ than single oral administration revealing an accumulation phenomena of asiatic acid during chronic treatment which was very well correlated to the *in vivo* transformation of asiaticoside to asiatic acid.

## 7. Pharmacological activities

### *7.1 Promotion of skin and bone healing*

In a study conducted using different extracts of CA, *viz.* petroleum ether, chloroform, alcoholic, propylene glycol, glycosidal and aqueous extracts, the topical administration of aqueous extract alone (suspended in 5% propylene glycol) promoted wound healing as evidenced by increase in collagen content and thickness of

epithelium [8] on experimentally induced open wounds in rats.

In another study, however, it was demonstrated that the alcoholic extract of CA (oral and topical) also improved the rate of wound healing in rats [9]. Asiaticoside stimulates the epidermis by activating the cells of malphigian layer in porcine skin, and by keratinization *in vitro*. Topical application of asiaticoside also promotes wound healing in rats and increases the tensile strength of newly formed skin. This is valuable in the treatment of hypertrophic scars and keloids. By decreasing the fibrosis in wound, asiaticoside prevents new scar formation. The mechanism of action appears to be two fold: by increasing the synthesis of collagen and acidic mucopolysaccharides and by inhibiting the inflammatory phase of hypertrophic scars and keloids. It has been further proposed that asiaticoside interferes with scar formation by increasing the activity of myofibroblasts and immature collagen [10].

Also, the studies conducted by Shukla *et al.* [11] confirm the wound healing activity of asiaticoside apart from validating the use of *C. asiatica* preparations in the Indian traditional system of medicine to promote wound healing. The studies proved the efficacy of asiaticoside in wound healing of normal as well as delayed healing models. It attributes the wound healing effect of the drug to the ability to increase hydroxyproline, tensile strength, collagen content and better epithelisation [11].

Topical application of aqueous extract has been reported to increase cellular proliferation and promote collagen synthesis at the wound site as evidenced by increase in DNA, protein, collagen content and tensile strength of granulation tissue [12]. The treated wound epithelialised faster and the rate of wound contraction was higher as compared to control. Among the various formulations (ointment, cream and gel) of the aqueous extract, the process of healing was better with gel formulation [12].

In another study, when twenty two patients with chronic infected skin ulcers were treated with a cream containing 1% extract of CA for 3 weeks, 17 of them showed complete healing while the rest showed improvement in healing [13]. A standardized extract of the herb was reported to treat indolent leg ulcers in clinical trials [14]. Local application of the extract to second and third degree burns expedited healing, prevented the shrinking and swelling caused by infection, and further inhibited hypertrophic scar formation [15]. A formulation containing asiaticoside as the main ingredient healed 64% of the soiled wounds and relieved chronic or recurrent atony that was resistant to the usual treatment [10].

*7.2 Effects on central nervous system*

A 70% ethanol extract of CA, administered intraperitoneally to mice has shown to produce anticonvulsant activity [16]. In albino rats, CA extracts have been found to have imipramine like antidepressant effect [17] and significant antistress activity comparable to diazepam [18]. Further more, another report also suggest the antianxiety effect of Centella which was comparable to diazepam as well as without affecting the behavioural despair [19].

On contrary, administration of CA was also shown to exert adverse effects such as sedation, hypotheramia, besides being ineffective in protecting from metrazol-induced seizures and electroshock seizures [20]. In another study, trained rats treated with extracts of CA showed dose dependent conditioned avoidance comparable to chlorpromazine. It has been suggested that the extract causes impairment of muscular coordination and has a tranquilizing effect [20].

In biochemical studies conducted by Nalini *et al* [21], urinary metabolites of central monoamines, with the exception of 3 methoxy-4 -hydroxyl phenyl glycol (MHPG), were found to be decreased with the treatment of CA. Similar decrease was also observed in brain homogenates indicating the overall decrease in the turnover of central monoamines explaining the possible mode of above mentioned CNS effects.

However, these findings are not in concordance with the previous reports where anticonvulsant activity of CA in rats was found to be accompanied with a significant increase in whole brain content of catecholamines and histamine and a significant decrease in acetyl choline levels based on the studies on neurochemistry of brains. [22].

The drug has been found to excert weak sedative, cardiodepressant and hypotensive effect [22]. In a double blind clinical trial, conducted on 30 children, it has been found to improve the cognitive functions in mentally retarded children. The patients in the study were free from epilepsy and other neurological conditions. The drug was administered for 12 weeks and the results indicate a significant improvement in both general ability and behavioural patterns [23].

*7.3 Antiulcer activity*

A small clinical trial involving fifteen patients has demonstrated the antiulcer activity after oral administration of the extract of CA at the dose level of 60 mg/kg daily. Approximately 93% of the patients exhibited a definite improvement in subjective symptoms and 73% of the ulcers were healed as measured by endoscopic and radiological observations [24].

In an experimental study on albino rats, CA has been found to produce antiulcer effect in cold restraint stress-induced gastric ulcer, aspirin-induced gastric ulcer and pyloric ligation-induced peptic ulcer models. The possible mechanism of action was proposed to be mediated through the enhancement of mucosal defensive factors [25]. However, the reports of Chatterjee *et al* (1992) suggest the possible involvement of GABA-mediated action in the antiulcer activity of CA [26].

*7.4 Antileprotic and antitubercular activities*

Oral administration of CA or asiaticoside and potassium chloride capsules has been reported to be effective against leprosy. In a clinical trial for the treatment of leprosy with CA for one year, improvement has been found to be faster as compared to dapsone. The drug was well tolerated by the patients and the therapeutic effect was comparable to dapsone [27]. Hydroxyasiaticoside, when injected to guinea pigs inoculated with Mycobacterium, it reduced the size and number of tubercular lesions in the liver, lungs, nerve ganglion and spleen [28].

*7.5 Management of venous insufficiency*

Clinical studies on CA in the treatment of venous disorders has demonstrated a positive therapeutic effect [29]. Treatment with a titrated extract of CA in patients suffering from venous insufficiency, showed significant improvement from venous distension and oedema as compared to controls [30].

*7.6 Anticancer and immunomodulatory activities*

Crude extract as well as purified extracts of CA significantly inhibited the proliferation of transformed cell lines and suppressed the multiplication of mouse lung fibroblast (L-929) cells. The antitumor effect of the crude extract of CA as well as the partially purified fraction was studied in both, *in vitro* short and long term chemosensitivity test systems and *in vivo* tumor models. The purified fraction inhibited the proliferation of transformed cell lines of

Ehrlich ascites tumor cells and Dalton's lymphoma ascites tumor cells more significantly than crude extract.

It also significantly suppressed the multiplication of mouse lung fibroblast cells in long term culture. *In vivo* administration of both extracts retarded the development of solid and ascites tumor and increased the lifespan of tumor bearing mice. Tritiated thymidine, uridine and leucine incorporation assays suggest that the purified fraction acts directly on DNA synthesis. However, no toxic effects were observed in normal human lymphocytes [31]. In another study with similar results, structure related antitumor effects were demonstrated to be mediated through stimulation of immune system [32].

The aqueous suspension of CA (100 mg/kg/ day, orally for 7 days) has been tested for immunostimulant activity in rats. Recombinant interferon-α2b was chosen for comparison and control studies were made simultaneously. These preliminary studies demonstrated immuno-stimulant property of CA that was 60% of that produced by interferon-α2b [33].

The structure related antitumor effects in mouse lung fibroblasts have been demonstrated to be through the modulation of immune system by various triterpenoid saponins as evidenced by lymphocyte transformation at very low concentrations (< 1-3 μg/ml) [32].

*7.7 Miscellaneous effects*

The effect of the whole plant powder on growth pattern and some biochemical constituents of blood and tissues was studied on albino rats fed on low protein diet (15%). The drug prevented the mortality rate due to gross protein deficiency. It increased the blood protein nitrogen and prevented the fatty infiltration of liver.

In another study, a double blind clinical trial was conducted in 43 normal adults to evaluate the rasayana effects of the drug. It has been found to increase the mean level of red blood cells, blood sugar, serum cholesterol, vital capacity and total protein. The increase in the haemoglobin percentage was quite high and statistically significant. The drug also increased the mean blood urea level and a moderate decrease in serum acid phosphatase activity was observed [34].

Crude extract of CA and constituents derived from it (glycosides) have been screened as oral antifertility agents in albino mice. These are reported to cause reduction in fertility in female mice. Saponins of the plant have shown spermicidal activity in human semen, in both the spot and JPPE test [35].

Stress is, an everyday phenomenon in an individuals life. Reactions to stressors may either precipitate and exacerbate diseases like hypertension, myocardial infarction, peptic ulcer, asthma, colitis and even diabetes [36]. Herbs with antistress activities like CA, (17) may be used as adjuvants in the management of diseases like diabetes. In a prospective double blind, randomized, placebo controlled study the psychopharmacological effects of CA were evaluated in diabetics. It has been found that the levels of stress, anxiety and depression were higher in diabetics, particularly in those with uncontrolled blood sugar. CA was found to improve the stress and depression in these patients. Thus, by modulation of psychoneuroimmune axis, these drugs may reduce the dose of insulin and hypoglycaemics and therefore, help in better management of diabetes [37].

**8. Adverse effects and toxicity**

Literature surveyal revealed paucity of data on toxicological investigations of CA. However, in a study reported by Anithal and Sirsi [38], the

alcoholic extract showed no any sign of toxicity or mortality up to a dose of 350 mg/kg, in rats. Asiaticosides have been implicated as possible skin carcinogens in rodents after repeated topical application [40]. Allergic contact dermatitis has been reported with topical application of CA [39].

**9. Precautions and Contraindications**

As no information is available concerning drug interactions, drug and laboratory test interactions, teratogenic/ non teratogenic effects on pregnancy, nursing mothers and paediatric use, as a precaution this drug should be avoided by pregnant and lactating mothers. This herb is contraindicated in individuals allergic to the plants of Apiaceae family.

**10. Conclusion**

A critical analysis of the literature screened for this review revealed that this herb finds widespread use in several traditional systems of medicine. Several of its traditional uses, like promotion of skin and bone healing, antiulcer activity and antileprotic effects, have now been supported by the scientific studies. The active principles present in the plant have been isolated and the pharmacological effects have been well correlated with the phytochemical constituents.

However, for several other uses, there is an urgent need for generation of adequate data through experimental and clinical studies. A greater number of studies should be focused on the levels of neurotransmitters, cytotoxic enzyme activities, DNA patterns and genetic control rather than concentrating merely on the gross effects induced by herbs.

Today, concurrent consumption of drugs from different streams of medicine is a common finding. However, authors could not find a single study addressing the problem of drug interaction, if any, with CA. Similarly, the documented data on the adverse drug reactions of this herb is also sparse. Further, the need today is to judicially utilize the advances in cellular biology and molecular pharmacology to validate the efficacy and safety of herbal drugs as well as to explain their mechanism of action.

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