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Pharmacological Review on *Centella asiatica*: A Potential Herbal Cure-all

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Abstract

In recent times, focus on plant research has increased all over the world. *Centella asiatica* is an important medicinal herb that is widely used in the orient and is becoming popular in the West. Triterpenoid, saponins, the primary constituents of *Centella asiatica* are manly believed to be responsible for its wide therapeutic actions. Apart from wound healing, the herb is recommended for the treatment of various skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis, diarrhoea, fever, amenorrhea, diseases of the female genitourinary tract and also for relieving anxiety and improving cognition. The present review attempts to provide comprehensive information on pharmacology, mechanisms of action, various preclinical and clinical studies, safety precautions and current research prospects of the herb. At the same time, studies to evaluate the likelihood of interactions with drugs and herbs on simultaneous use, which is imperative for optimal and safe utilization of the herb, are discussed.

Keywords: *Centella asiatica*, description, herb-drug interactions, pharmacology of *Centella asiatica*, preclinical and clinical studies, side effects, therapeutic uses

Plants have been used as treatments for thousands of years, based on experience and folk remedies and continue to draw wide attention for their role in the treatment of mild and chronic diseases. In recent times, focus on plant research has increased all over the world and a large body of evidence has been accumulated to highlight the immense potential of medicinal plants used in various traditional systems of medicine[1–3]. *Centella asiatica* (CA) is a very important medicinal herb used in the orient[4], which is also becoming popular in the West[5]. Commonly known as *mandukparni* or Indian pennywort or *jalbrahmi*, it has been used as a medicine in the Ayurvedic tradition of India for thousands of years and listed in the historic *'Sushruta Samhita'*, an ancient Indian medical text[6,7]. The herb is also used by the people of Java and other Indonesian islands. In China, known as *gotu kola*, it is one of the reported "miracle elixirs of life" known over 2000 years ago[7]. CA or *gotu kola* should not be confused with kola nut as it does not contain any caffeine and has not been shown to have stimulant properties. In the nineteenth century, CA and its extracts were incorporated into the Indian pharmacopoeia, wherein in addition to wound healing, it was recommended for the treatment of various skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis, diarrhoea, fever, amenorrhea, and diseases of the female genitourinary tract[8]. Despite large number of studies reported over the past decades on the evaluation of biologically active components and their mechanisms of action, the outcome of these studies is still unsatisfactory. Although there have been several claims regarding the underlying mechanisms involved in the biological actions of this herb, more scientific data are needed to justify its ever increasing use. Therapeutic potential of this plant in terms of its efficacy and versatility is such that further detailed research would appear momentous. The present review incorporated a detailed account of the plant, stressing its therapeutic uses, pharmacology, mechanisms of action based on preclinical and clinical studies, safety issues along with the current research potential of the herb. A high quality and reliable medical information from the internet was retrieved only from the Health-on-Net (HON) conduct-certified and accredited websites like Entrez PubMed (Medline), CAM-PubMed, Allied and complementary medicine database, Natural Medicine Comprehensive Database, Embase and Cochrane library. The databases were searched up to the year 2009 for the latest information on the herb.

Description of the plant:

Centella asiatica (CA), a clonal, perennial herbaceous creeper belonging to the family *Umbellifere* (*Apiceae*) is found throughout India growing in moist places up to an altitude of 1800 m. It is found in most tropical and subtropical countries growing in swampy areas, including parts of India, Pakistan, Sri Lanka, Madagascar, and South Africa and South pacific and Eastern Europe. About 20 species related to CA grow in most parts of the tropic or wet pantropical areas such as rice paddies, and also in rocky, higher elevations[4]. It is a tasteless, odourless plant that thrives in and around water. It has small fan-shaped green leaves with white or light purple-to-pink or white flowers and it bears small oval fruit (fig. 1). The whole plant is used for medicinal purposes[9]. It is widely used as a blood purifier as well as for treating high blood pressure, for memory enhancement and promoting longevity. In Ayurveda, CA is one of the main herbs for revitalizing the nerves and brain cells. Eastern healers relied on CA to treat emotional disorders, such as depression, that were thought to be rooted in physical problems[10,11]. In the Western medicine, during the middle of the twentieth century, CA and its alcohol extracts reported to have shown positive results in the treatment of leprosy[12].

Fig. 1
Centella asiatica herb

Active constituents:

The primary active constituents of CA are saponins (also called triterpenoids), which include asiaticosides, in which a trisaccharide moiety is linked to the aglycone asiatic acid, madecassoside and madasiatic acid[13]. These triterpene saponins and their sapogenins are mainly responsible for the wound healing and vascular effects by inhibiting the production of collagen at the wound site. Other components isolated from CA, such as brahmoside and brahminoside, may be responsible for CNS and uterorelaxant actions, but are yet to be confirmed by clinical studies. Crude extract containing glycosides isothankuniside and thankuniside showed antifertility action in mice[14,15]. Centelloside and its derivatives are found to be effective in the treatment of venous hypertension. In addition, the total extract contains plant sterols, flavonoids, and other components with no known pharmacological activity[16], namely, abundant tannins (20-25%), essential acid (0.1% with beta-chariophylen, trans-beta-pharnesen and germachrene D), phytosterols (campesterol, sitosterol, stigmasterol), mucilages, resins, free aminoacids (alanine, serine, aminobutyrate, aspartate, glutamate, lysine and treonine), flavonoids (derivates of chercetin and kempferol), an alkaloid (hydrochotine), a bitter component (vallerine), fatty acids (linoleic acids, linolnelic, oleic, palmitic and stearic acids).

MECHANISMS OF ACTIONS BASED ON PRECLINICAL STUDIES

Wound healing:

The CA extracts (CAE) have been used traditionally for wound healing and the research has been increasingly supportive for these claims[8]. A preclinical study reported that various formulations (ointment, cream, and gel) of an aqueous CAE applied to open wounds in rats (3 times daily for 24 days) resulted in increased cellular proliferation and collagen synthesis at the wound site, as shown by an increase in collagen content and tensile strength[17]. The authors found that the CAE-treated wounds epithelialized faster and the rate of wound contraction was higher when compared to the untreated control wounds. 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[18]. Asiaticoside, a constituent in CA, has been reported to possess wound healing activity by increasing collagen formation and angiogenesis[19,20]. Apart from showing a stimulation of the collagen synthesis in different cell types, the asiaticoside were shown to increase the tensile strength of the newly formed skin, furthering the healing of the wounds. Also, it was shown to inhibit the inflammatory process which may provoke hypertrophy in scars and improves the capillary permeability[19,20]. In one laboratory animal study, the effects of asiaticoside on antioxidant levels were examined, as antioxidants have been reported to play a role in the wound healing process[21]. The authors concluded that asiaticosides may have enhanced the induction of antioxidants at an initial stage of wound healing, but continued application of the preparation seemed not to increase the antioxidant levels in wound healing. The activity of asiaticoside has been studied in normal as well as delayed-type wound healing[22]. In guinea pig punch wounds topical applications of 0.2% solution of asiaticoside produced 56% increase in hydroxyproline, 57% increase in tensile strength, increased collagen content and better epithelisation. In streptozotocin diabetic rats, where healing is delayed, topical application of 0.4% solution of asiaticoside over punch wounds increased hydroxyproline content, tensile strength, collagen content and epithelisation thereby facilitating the healing. Asiaticoside was active by the oral route also at 1 mg/kg dose in the guinea pig punch wound model. It promoted angiogenesis in the chick chorioallantoic membrane model at 40 µ/disk concentration. In one study, effects of oral and topical administration of an alcoholic extract of CA on rat dermal wound healing were evaluated[22]. The extract increased cellular proliferation and collagen synthesis at the wound site, as evidenced by increase in DNA, protein and collagen content of granulation tissues. Quicker and better maturation and cross linking of collagen was observed in the extract-treated rats, as indicated by the high stability of acid-soluble collagen and increase in aldehyde content and tensile strength. The extract treated wounds were found to epithelialize faster and the rate of wound contraction was higher, as compared to control wounds. These results indicated that CA produced different actions on the various phases of wound repair by exhibiting significant wound healing activity in normal as well as delayed healing models[23].

Venous insufficiency:

One of primary effects of CA was postulated to be on connective tissues by strengthening the weakened veins[24]. It was postulated that CA might assist in the maintenance of connective tissue[25]. In the treatment of scleroderma, it might also assist in stabilizing connective tissue growth, reducing its formation as it reportedly stimulated the formation of hyaluronidase and chondroitin sulfate, as well as exerted a balancing effect on the connective tissue[25]. CA was reported to act on the connective tissues of the vascular wall, being effective in hypertensive microangiopathy and venous insufficiency and decreasing capillary filtration rate by improving microcirculatory parameters[26].

Sedative and anxiolytic properties:

CA was described to possess CNS effects in Indian literature such as stimulatory-nervine tonic, rejuvenant, sedative, tranquilizer and intelligence promoting property[27]. It has been traditionally used as a sedative agent in many Eastern cultures; the effect was postulated mainly due to the brahmoside and brahminoside constituents, while the anxiolytic activity is considered to be, in part due to binding to cholecystokinin receptors (CCK_B), a group of G protein coupled receptors which bind the peptide hormones cholesystokinin (CCK) or gastrin and were thought to play a potential role in modulation of anxiety, nociception, memory and hunger in animals and humans[28].

Antidepressant properties:

The antidepressant effects of total triterpenes from CA on the immobility time in forced swimming mice and concentration of amino acid in mice brain tissue was observed. In the study, imipramine and total triterpenes from CA reduced the immobility time and ameliorated the imbalance of amino acid levels confirming the antidepressant activity of CA[29]. The same authors investigated the possible antidepressant effect of total triterpentes of CA by measuring the corticosterone levels in mice brain[30]. The contents of monoamine neurotransmitters and their metabolites in rats cortex, hippocampus and thalamus were evaluated wherein significant reduction of the corticosterone level and increase of the contents of 5-HT, NE, DA and their metabolites 5-HIAA, MHPG in rat brain were observed which further strengthened the postulated involvement of total triterpenes of CA in ameliorating the function of HPA axis and increasing the contents of monoamine neurotransmitters for its antidepressant effects.

Antiepileptic properties:

Asian CA increases the cerebral levels of GABA, which explains its traditional use as anxiolytic and anticonvulsant. The isolated steroids from the plant have been used to treat leprosy[31]. In one study, the effects of aqueous CAE (100 and 300 mg/kg) were evaluated on the course of kindling development, kindling-induced learning deficit and oxidative stress markers in pentylenetetrazole (PTZ) kindled rats[32]. Passive avoidance test and spontaneous locomotor activity, after 24 and 48 h after administration of PTZ, and oxidative stress parameters like malondialdehyde (MDA) and glutathione were carried out in the whole brain of animals. The administration of CA (300 mg/kg, p.o) decreased the PTZ-kindled seizures and showed improvement in the learning deficit induced by PTZ kindling as evidenced by decreased seizure score and increased latencies in passive avoidance behaviour. The findings suggested the potential of aqueous CAE as adjuvant to antiepileptic drugs with an added advantage of preventing cognitive impairment. The hydroalcoholic extract of CA leaves was also subjected to pharmacological screening using various experimental models and was found to show protective action against increase in intracranial electric stimulation (ICES) and chemo-convulsions, which includes pentylenetetrazol-induced convulsions, pentylenetetrazol-kindled seizures, and strychnine-induced opisthotonus tonic convulsions on oral administration[33]. It also showed a reduction in formation of lipid peroxidation products, reduction in spontaneous motor activity, potentiation in diazepam withdrawal-induced hyperactivity, hypothermia, and potentiation of pentobarbitone sleeping time. The extract (200 mg/kg body weight) completely inhibited pentylenetetrazol-induced convulsions. In pentylenetetrazol-kindled seizures and strychnine-induced convulsions, the extract showed protection at a dose of 100 mg/kg body weight. The doses of the extract selected for remaining studies were based on pilot studies, animal model used, and so forth. These findings suggested its potential anticonvulsant as well as antioxidant, and CNS depressant actions[33].

Cognitive and antioxidant properties:

CA is known to re-vitalize the brain and nervous system, increase attention span and concentration and combat aging[8]. A study demonstrated cognitive-enhancing and anti-oxidant properties of CA in normal rats. The effect of an aqueous CA extracts (100, 200 and 300 mg/kg for 21 days) was evaluated in intracerebroventricular (i.c.v.) streptozotocin (STZ)-induced cognitive impairment and oxidative stress in rats[34]. The rats treated with CA showed a dose-dependent increase in cognitive behaviour in passive avoidance and elevated plus-maze paradigms. A significant decrease in MDA and an increase in glutathione and catalase levels were observed only in rats treated with 200 and 300 mg/kg CA. As the oxidative stress or an impaired endogenous anti-oxidant mechanism is an important factor as implicated in Alzheimer>s disease (AD), cognitive deficits seen in the elderly and the i.c.v. STZ in rats has been linked to sporadic AD in humans. The cognitive impairment was associated with free radical generation in the model in the above study. The findings reported in above study suggested the potential efficacy of CA in preventing the cognitive deficits, as well as the oxidative stress[34]. To throw more light on mechanism of these neuroprotection by CA, one recent study reported that the phosphorylation of cyclic AMP response element binding protein (CREB) was enhanced in both a neuroblastoma cell line expressing amyloid beta 1-42 (A beta) and in rat embryonic cortical primary cell culture[35]. In addition, the contribution of two major single components to the enhanced CREB phosphorylatioin was examined. Furthermore, inhibitors were applied in this study revealed that ERK/RSK signalling pathway (extra cellular signal-regulated kinase-ribosomal S6 kinase) might mediate this effect of CA extract. In another study, while, oral treatment with 50 mg/kg/day of crude methanol extract of CA for 14 days significantly increased the anti-oxidant enzymes, like superoxide dismutase (SOD), catalase and glutathione peroxidase (GSHPx) in lymphoma-bearing mice, the anti-oxidants like glutathione (GSH) and ascorbic acid were decreased in the animals[36]. In one study, derivatives of asiatic acid derivatives were shown to exert significant neuroprotective effects on cultured cortical cells by their potentiation of the cellular oxidative defence mechanism. Therefore, these agents were proved to be efficacious in protecting neurons from the oxidative damage caused by exposure to excess glutamate[37]. Another study demonstrated the protective effects of asiaticoside derivatives against beta-amyloid neurotoxicity when tested on B103 cell cultures and hippocampal slices. Out of 28 of the asiaticoside derivatives three components, including asiatic acid, showed a strong inhibition of beta-amyloid- and free radical-induced cell death. These derivatives may be candidates for a treatment of Alzheimer>s disease that protects neurons from beta-amyloid toxicity[38].

Gastric ulcer:

A laboratory study was reported in which aqueous extract of CA was found to be effective in inhibiting gastric lesions induced by ethanol administration[39]. The authors concluded that the CA extract presumably strengthened the gastric mucosal barrier and reduced the damaging effects of free radicals. Animal studies showed that CA extracts inhibited gastric ulceration induced by cold and restraint stress, in rats. The antiulcer activity was compared to famotidine (H_2-antagonist) and sodium valproate (antiepleptic or antiseizure). Both the drugs and the herb extract showed a dose-dependent reduction of gastric ulceration, which, except for the antiulcer effect of famotidine, could be reversed with bicucullin methiodide (specific GABAA antagonist)[40]. It was postulated that CAE, which increased GABA levels in the brain, protected the rats against the cold restraint ulceration. Moreover, it is known that GABA and its agonists inhibit the central cholinergic action by affecting the turnover rate of acetylcholine in the rat brain[41]. Yet, another study was conducted to evaluate the possible anti-ulcerogenic activity of fresh juice of CA against ethanol-, aspirin-, cold-restraint stress- and pyloric ligation induced gastric ulcers in rats. The drug given orally in doses of 200 and 600 mg/kg twice daily for five days, showed significant protection against all the above experimental ulcer models and the results were comparable with those elicited by sucralfate (SF, 250 mg/kg, p.o., BD×5 days). CA extracts showed little or no effect on offensive acid-pepsin secretion. However, at 600 mg/kg it significantly increased gastric juice mucin secretion and increased the mucosal cell glycoproteins signifying increase in cellular mucus. It also decreased cell shedding indicating fortification of mucosal barrier. Author concluded that the ulcer protective effect of CAE may be due to strengthening of the mucosal defensive factors[42]. One study showed that CA and its constituents, asiaticosides have an anti-inflammatory property that was brought about by inhibition of nitric oxide (NO) and thus facilitating ulcer healing[43]. Some other researchers also showed the efficacy of CA through preclinical and clinical studies for healing gastric ulcers[44,47]. CA has also been investigated to demonstrate its role in periodontal therapy[48].

Antinociceptive and antiinflammatory properties:

The effects of CA upon pain (antinociception) and inflammation in rodent models were reported[49]. The antinociceptive activity of the aqueous CAE (10, 30, 100 and 300 mg/kg) was studied using acetic acid-induced writhing and hot-plate method in mice[49], while the antiinflammatory activity of CA was studied by prostaglandin E2-induced paw edema in rats[49]. The aqueous CAE revealed significant antinociceptive activity with both the models similar to aspirin but less potent than morphine and significant antiinflammatory activity comparable to mefenamic acid. These results suggested that the aqueous CA extracts possesses antinociceptive and antiinflammatory activities which justified the traditional use of this plant in the treatment of inflammatory conditions or rheumatism[50]. Recently, antirheumatoid arthritic effect of madecassoside in type II collagen-induced arthritis (CIA) in mice was studied to investigate the therapeutic potential and underlying mechanisms of madecassoside on CIA[51]. Madecassoside (10, 20 and 40 mg/kg), orally administered from the day

of the antigen challenge for 20 consecutive days, dose-dependently alleviated the severity of the disease based on the reduced clinical scores, and elevated the body weights of mice. Also, a histopathological examination indicated that madecassoside alleviated infiltration of inflammatory cells and synovial hyperplasia as well as provided protection against joint destruction. Moreover, madecassoside reduced the serum level of antiCII IgG, suppressed the delayed type hypersensitivity against CII and moderately suppress CII-stimulated proliferation of lymphocytes from popliteal lymph nodes in CIA mice. *In vitro*, madecassoside was proved to be ineffective in the activation of macrophages caused by lipopolysaccharide[51]. It was concluded in the study that madecassoside substantially prevented mouse CIA, and might be the major active constituent of CA responsible for its clinical uses in rheumatoid arthritis and that the underlying mechanisms of action may be mainly through regulating the abnormal humoral and cellular immunity as well as protecting from joint destruction[51].

Radioprotection:

Previous studies have suggested that CA could be useful in preventing radiation-induced behavioural changes during clinical radiotherapy[52,53]. The plant extracts were also tested for its radioprotective properties at a sublethal dose (8 Gy) of Co 60 gamma radiation[52]. A 100 mg/kg dose increased the survival time of the mice significantly. Body weight loss of the animals in the drug treated group was significantly less in comparison with the animals that were given radiation only[53].

Miscellaneous uses:

A study reported the intracellular activities of an aqueous CAE against herpes simplex viruses, *in vitro*, containing both anti HSV-1 and antiHSV-2 activities[54,55]. Both the crude extract and purified fractions showed cytotoxicity against Ehrlich ascites and Dalton>s lymphoma ascites tumour cells, used in the study in a concentration-dependent manner. However, no cytotoxic effects were detected against normal cell lines. The oral administration of the extracts (crude or purified) retarded the development of solid and ascites tumours in mice[56]. Antimycotic activity of CA was also reported[57]. The efficacy of CA in the treatment of depression, anxiety, and sleep disorders have been tested on small animals and are believed to be associated with its brahmoside and brahminoside constituents or saponin glycosides[58].

CLINICAL STUDIES

Most of the clinical studies on Asian CA have been realized with alcoholic or aqueous extracts. The TECA extracts (titrated extracts of Asian CA and TTFCA (triterpenic total fraction of Asian CA) are combinations of asiatic acid (30%), madecasic acids (30%) and asiaticoside (40%). The TTF extract (triterpenic total fraction) consists of Asian CA and madecasic acids (60%) in a relation not clearly defined yet, in combination with asiatichoside (40%). Both *in vivo* clinical studies and human monolayer cell culture experiments have concluded that asiatic acid influences collagen synthesis. The selective action of the local application of triterpenoid fraction of CAE for wound healing and emphasized the role of asiaticoside in the increased levels of antioxidants (enzymatic and nonenzymatic), which were also implied for the accelerated wound healing[59–60]. It is now known that angiogenesis plays an important role in wound healing since the newly formed blood vessels help the hypoxic wounds to attain normoxic conditions. Asiaticoside prompted angiogenesis in both *in vivo* and *in vitro* models[61]. In cases of vascular injury, thrombosis, acute myocardial infarction, and other peripheral vascular diseases, a higher number of circulating endothelial cells was detected. For example, in one study, patients with post phlebetic syndrome (PPS) showed a greater number of circulating endothelial cells compared to the normal subjects[62]. During a three-week treatment with CA triterpenic fraction (CATF), PPS patients who received 90 mg CATF daily in three divided dosages showed a statistical significant decrease in circulating endothelial cells, thereby indicating the effectiveness of CA in protecting the integrity of vascular intima. The lower number of circulating endothelial cells was attributed to the protective effect of CATF on vascular intima integrity[62]. The extract of CA was tested on 94 patients suffering from venous insufficiency of the lower limbs[63]. The patients were divided into three groups, each treated with TECA (120 mg/day, 60 mg/day or placebo) for two months. A statistical significant difference in favour of TECA groups was observed in the parameters checked for lower limbs and edema; also the overall evaluation was shown positive for the TECA treated groups compared to the placebo[63]. CATF 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. The additional 10 control subjects were treated with 60 mg/day. After four weeks of treatment significant improvements were observed in a concentration-dependent manner in the parameters tested, such as filtration rate, ankle edema, and ankle circumference. No significant changes were observed in placebo and control subjects treated with CATF[64]. In another double-blind clinical trial involving 87 patients with chronic venous hypertensive microangiopathy, two dosage forms of CATF (30 mg/day and 60 mg/day) were applied for 60 days and no unwanted effects were observed. The results also confirmed the efficacy of CATF in a dose-dependent manner[65]. The effects of the CATF on enzymes involved in mucopolysaccharide metabolism supported the hypothesis that the extract acts on basic metabolism in the connective tissues of the vascular wall[66]. The levels of basal serum uronic acid and enzymes involved in mucopolysaccharide metabolism (beta-glucuronidase, beta-N-acetylglucosaminidase, and arylsulfatase) were elevated in patients with varicose veins, indicating an increased muco-polysaccharide turnover. After treatment (60 mg/day for three months) the above enzyme levels fell progressively[66].

A double-blind, placebo-controlled study was conducted to check the effects of an oral standardized CA product in two doses (30 mg bid and 60 mg bid) in 87 patients with chronic venous hypertensive microangiopathy[67]. Microcirculatory parameters were shown to be improved as compared to placebo in dose dependent manner, with the higher dose improving symptoms more significantly. Another study reported the beneficial effects of an oral standardized CA product (60 mg three times a day over a 2 month period) in vascular permeability and microcirculation as assessed by laser Doppler flowmetry[68]. The results showed a combined improvement of the microcirculation and capillary permeability in all patients (10 normal subjects, 22 patients with moderate, superficial venous hypertension, and 12 patients with postphlebitic limbs and severe venous hypertension). Another study in patients with severe venous hypertension due to deep venous disease reported that a standardized CA extract was acutely effective in reducing capillary filtration and edema in individuals with venous hypertensive microangiopathy[69]. CA preparations were found helpful in decreasing the stretch marks (striae gravidarum) that many women develop during pregnancy[70]. A placebo-controlled study of 100 pregnant women compared application of a cream containing a CAE, vitamin E (alpha tocopherol), and collagen-elastin hydrolysates to placebo[70]. Application of the compounded cream was associated with fewer women developing stretch marks than in placebo. Application of topical CA preparations were shown to be beneficial in decreasing the scarring seen during wound healing, appearing to be related to the stimulation of maturation of the scar by the production of type I collagen and the resulting decrease in the inflammatory reaction and myofibroblast production[71]. In a randomized, double-blind, vehicle-controlled, half-side comparison study, undertaken to determine if it could also improve mild-to-moderate atopic dermatitis in adults, eighty-eight participants were randomly applied the treatment ointment and the placebo control to either the left or right side of the body for 4 weeks (2 applications per day) after which erythema, edema, oozing, and excoriation were assessed[72]. No significant improvements were detected in the treatment group as compared to the control group; however, further analysis of patients living in colder climates showed a significant

improvement in the treated areas. Because the ointment consisted of the combination of herbs, it was suggested that further studies using each individual herb and studies using a parallel group design were required to be performed.
In one recent randomized, placebo-controlled, double-blind study, 28 participants (< 61 years of age) received either CA extracts (250, 500, or 750 mg daily) or placebo in order to determine the effect of CA on cognitive function and mood[73]. In the study, after 2 months, cognitive function (as assessed by event-related potential and the computerized assessment battery test) and mood (using Bond-Lader visual analogue) was determined. The greatest improvements in mood and cognitive function were detected in those receiving the 750 mg dose of CA extract. A double-blind, placebo-controlled study investigated the anxiolytic activity of CA in human subjects[74]. The authors concluded that the findings suggested CA's anxiolytic activity in humans. Very recently, a study was conducted in sixty elderly subjects in age group 65 and above, using diagnostic tools like Mini Mental State Examination scoring (MMSE scoring), wherein activities of daily living and Yesavage geriatric depression scale were evaluated[75]. The mean MMSE scoring showed significant improvement after administration of CA for 6 months in elderly with mild cognitive impairment (MCI) at dosage of 500 mg twice a day (1000 mg daily). A favourable improvement is observed in depression and other age related conditions like Hypertension, peripheral neuritis, insomnia, loss of appetite, constipation indicative of multiple useful clinical effects of CA especially in the age-related cognitive decline in elderly.

Precautions and safety:

CA has no known toxicity in recommended doses. Side effects are rare but may include skin allergy and burning sensations (with external use), headache, stomach upset, nausea, dizziness, and extreme drowsiness which tend to occur with high doses of the herb. The fresh plant may have a low potential for skin irritation. A Contact dermatitis has been reported on a few occasions using topical preparations[76]. Subcutaneous injections can trigger allergic reactions, cause pain at the injection site, or cause discoloration. Side effects occur less often when using intramuscular injections. Orally consuming an excessive amount of CA (i.e., overdose) can cause headaches and transient unconsciousness. Also, it is postulated that chronic treatment may prevent women from becoming pregnant by causing spontaneous abortion[77]. As there is little or no information regarding the safety of this herb during breast feeding, nursing mothers are advised to refrain from taking this herb. During prolonged treatment, especially with higher doses, the metabolism of active constituents slows down and can produce toxicity, so it was suggested that this pharmacokinetic phenomena should be considered during pharmacotherapy for effective and safe treatment[78]. The use of CA for more than 6 weeks is not recommended in the literature. People taking the herb for an extended period of time (up to 6 weeks) should take a 2-week break before taking the herb again. The standardized CA extracts and asiaticoside were well tolerated in experimental animals especially by oral route. Asiaticoside did not show any sign of toxicity up to the dose of 1 mg/kg after oral administration, whereas the toxic dose by intramuscular application reported for mice and rabbits was 40-50 mg/kg[79].

Herb-drug interactions:

There have been no reports documenting negative interactions between CA and medications to date. Since high doses of CA can cause sedation, it was warned that individuals should refrain from taking this herb with medications that promote sleep or reduce anxiety[80]. Theoretically, CA was postulated to interfere with blood glucose levels and thus also possibly interfere with the existing hypoglycaemic therapy and cholesterol lowering agents[81].

Dosage:

A typical daily dose of CA reported was approximately 600 mg of dried leaves or infusion, single-dose capsules (300 mg to 680 mg, thrice daily), a 10-mg concentrated extract, also available in capsules. Other preparations include Madecassol tablets 10 mg 3 times daily, tincture 1 ml, and Emdecassol ointment twice daily[10]. Dried *gotu kola* leaf as a tea, by adding 1-2 teaspoons (5-10 g) to about 2/3 cup (150 ml) of boiling water and allowing it to steep for 10 to 15 min and three cups (750 ml) were usually suggested per day and fluid extract (1/2-1 teaspoon equivalent to 3-5 ml/day or a tincture (2-4 teaspoons equivalent to 10-20 ml per day) are sometimes recommended[8]. The standardized CA extract containing up to 100% total saponins (triterpenoids), 60 mg once or twice per day, are frequently used in modern herbal medicine[8].

Current findings and future prospects:

The present review is indicative of multiple useful clinical effects of *Centella asiatica* especially in the age-related cognitive decline. Further long-term studies will help determine the exact mechanism by which CA influences age-related changes in mood and cognitive function. Also the purported anxiolytic activity of CA is intriguing in view of the proposed involvement of cholecystokinin (CCK) in the pathophysiology of fear and anxiety. However, the mechanism of action and possible toxicity needs to be further investigated in a large sample which may bring to the light, the precise mechanisms for ameliorating many other CNS related conditions like depression and sleep disorders apart from anxiety. Moreover, more double blind randomized clinical trials are needed for investigating its sedative, analgesic, antidepressive, antiviral and immunomodulatory effects that have been demonstrated experimentally in animals.
Currently, a pilot study is going on by National Centre for Complementary and Alternative Medicine (NCCAM) in Oregon U.S.A, to investigate the safety, tolerability and effectiveness of *Centella asiatica* selected triterpenes (CAST)[82]. In this Phase II randomized, double blind study CA is being evaluated as a treatment for diabetic neuropathy using primary outcome measure as total neuropathic symptom score and secondary outcomes as neurological disability score, nerve conduction measurements and quantitative sensory testing. One recent study described protective effect of CA extracts against colchicine induced cognitive impairment and associated oxidative damage in rats[83]. In the study, chronic treatment with CA extracts (150 and 300 mg/kg, p.o.) for a period of 25 days, beginning 4 days prior to colchicine administration, significantly attenuated colchicine-induced memory impairment and oxidative damage, besides, significantly reversing the colchicines administered increase in acetylcholinesterase activity[83]. Another current study assessed the antioxidant property in elderly subjects and confirmed the beneficial effects of CAE (at doses of 500 and 750 mg per day) in elderly patients for 90 days, where, the CAE improved the strength especially in the lower extremities of the elderly[84]. The study also proved the role of CAE as a natural resource for vigor and strength increase, in healthy elderly persons.

CONCLUSIONS

The therapeutic potential of this plant in terms of its efficacy and versatility is such that further detailed research appears crucial. The growing number of herbal preparations in the market, including CA, raised the possibility of complications related to improper use of these products, or the lack of medical supervision along with the likelihood of interactions with the drugs and herbs on simultaneous use. Several of the recent cases reported to the special Nutritionals adverse event monitoring System indicated the importance of providing patient counselling on the use of herbal preparations.

Footnotes

Gohil, *et al*.: Review on *Centella asiatica*

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