

Selected Published Scientific References for Centella asiatica

In relation to its effects in dermatology and on the venous circulatory system

Altern Med Rev. 2007 Mar;12(1):69-72.

Centella asiatica - Monograph.

Centella asiatica (also known as gotu kola and *Hydrocotyle asiatica*) is a perennial, herbaceous creeper with kidney-shaped leaves, found in India, Sri Lanka, Madagascar, South Africa, Australia, China, and Japan. *Centella* prefers to grow in shady, moist, or marshy areas. *Centella* contains several active constituents, of which the most important are the triterpenoid saponins, including asiaticoside, centelloside, madecassoside, and asiatic acid. In addition, *Centella* contains other components, including volatile oils, flavonoids, tannins, phytosterols, amino acids, and sugars. *Centella* has several pharmacological actions, based primarily on in vivo experiments. After oral and topical administration in rats, increased cellular hyperplasia and collagen production was noted at the site of injury, measured by increased granulation tissue levels of DNA, protein, total collagen, and hexosamine. More rapid maturation and cross-linking of collagen were seen in animals treated with the herbal extract, as evidenced by elevated stability of acid-soluble collagen and increases in aldehyde content and tensile strength. Compared to control wounds, rats treated with gotu kola had a higher degree of epithelialization and a significantly more rapid rate of wound contraction. In addition to improving wound healing, *Centella* may also have an effect on connective tissue of varicosities. PMID: 17397269

Int J Low Extrem Wounds. 2006 Sep;5(3):137-43.

Effect of Centella asiatica L (Umbelliferae) on normal and dexamethasone-suppressed wound healing in Wistar Albino rats.

Shetty BS, Udupa SL, Udupa AL, Somayaji SN.

Department of Biochemistry, Melaka Manipal Medical College, India.

Centella asiatica is a reputed medicinal plant used in the treatment of various skin diseases in the Indian system of medicine. The objective of the study presented in this article was to evaluate the wound-healing potential of the ethanolic extract of the plant in both normal and dexamethasone-suppressed wound healing. The study was done on Wistar albino rats using incision, excision, and dead space wounds models. The extract of *C. asiatica* significantly increased the wound breaking strength in incision wound model compared to controls ($P < .001$). The extract-treated wounds were found to epithelize faster, and the rate of wound contraction was significantly increased as compared to control wounds ($P < .001$). Wet and dry granulation tissue weights, granulation tissue breaking strength, and hydroxyproline content in a dead space wound model also increased at statistically significant levels as shown. The extract of the leaves had the effect of attenuating the known effects of dexamethasone healing in all wound models ($P < .001$, $P < .05$). The results indicated that the leaf extract promotes wound healing significantly and is able to overcome the wound-healing suppressing action of dexamethasone in a rat model. These observations were supported by histology findings.

PMID: 16928669

Mol Cell Biochem. 2007 Jan;294(1-2):55-63. Epub 2006 Jun 20.

Adriamycin induced myocardial failure in rats: protective role of Centella asiatica.

Gnanapragasam A, Yogeeta S, Subhashini R, Ebenezar KK, Sathish V, Devaki T.

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Generation of reactive oxygen species and mitochondrial dysfunction has been implicated in adriamycin induced cardiotoxicity. Mitochondrial dysfunction is characterized by the accumulation of oxidized lipids, proteins and DNA, leading to disorganization of mitochondrial structure and systolic failure. The present study was aimed to evaluate the efficacy of *Centella asiatica* on the mitochondrial enzymes; mitochondrial antioxidant status

in adriamycin induced myocardial injury. Adriamycin (2.5 mg/kg body wt., i.p.) induced mitochondrial damage in rats was assessed in terms of decreased activities ($p < 0.05$) of cardiac marker enzymes (lactate dehydrogenase, creatine phosphokinase, amino transferases), TCA cycle enzymes (isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, malate dehydrogenase, respiratory marker enzymes (NADH-dehydrogenase, cytochrome-C-oxidase), mitochondrial antioxidant enzymes (GPx, GSH, SOD, CAT) and increased ($p < 0.05$) level of lipid peroxidation. Mitochondrial damage was confirmed by transmission electron microscopic examination. Pre-co-treatment with aqueous extract of *Centella asiatica* (200 mg/kg body wt, oral) effectively counteracted the alterations in mitochondrial enzymes and mitochondrial defense system. In addition, transmission electron microscopy study confirms the restoration of cellular normalcy and accredits the cytoprotective role of *Centella asiatica* against adriamycin induced myocardial injury. Our results demonstrated elevated oxidative stress and mitochondrial dysfunction in adriamycin treated rats. Moreover, on the basis of our findings it may be concluded that the aqueous extract of *C. asiatica* not only possesses antioxidant properties but it may also reduce the extent of mitochondrial damage. PMID: 16786185

Planta Med. 2006 Mar;72(4):324-8.

Asiaticoside induces human collagen I synthesis through TGFbeta receptor I kinase (TbetaRI kinase)-independent Smad signaling.

Lee J, Jung E, Kim Y, Park J, Park J, Hong S, Kim J, Hyun C, Kim YS, Park D.

Biospectrum Life Science Institute, Gunpo City, Gyunggi Do, Korea.

Skin aging appears to be principally related to a decrease in the levels of type I collagen, the primary component of the skin dermis. Asiaticoside, a saponin component isolated from *Centella asiatica*, has been shown to induce type I collagen synthesis in human dermal fibroblast cells. However, the mechanism underlying asiaticoside-induced type I collagen synthesis, especially at a molecular level, remains only partially understood. In this study, we have attempted to characterize the action mechanism of asiaticoside in type I collagen synthesis. Asiaticoside was determined to induce the phosphorylation of both Smad 2 and Smad 3. In addition, we detected the asiaticoside-induced binding of Smad 3 and Smad 4. In a consistent result, the nuclear translocation of the Smad 3 and Smad 4 complex was induced via treatment with asiaticoside, pointing to the involvement of asiaticoside in Smad signaling. In addition, SB431542, an inhibitor of the TGFbeta receptor I (TbetaRI) kinase, which is known to be an activator of the Smad pathway, was not found to inhibit both Smad 2 phosphorylation and Type 1 collagen synthesis induced by asiaticoside. Therefore, our results show that asiaticoside can induce type I collagen synthesis via the activation of the TbetaRI kinase-independent Smad pathway. PMID: 16557473

Phytomedicine. 2006 Nov;13(9-10):668-76. Epub 2006 Feb 20.

Evaluation of anxiolytic properties of Gotukola--(*Centella asiatica*) extracts and asiaticoside in rat behavioral models.

Wijeweera P, Arnason JT, Koszycki D, Merali Z.

Ottawa-Carleton Institute of Biology, University of Ottawa Institute of Mental Health Research, Royal Ottawa Hospital, Canada.

The ayurvedic medicinal plant Gotukola (*Centella asiatica*) was evaluated for its anxiolytic properties. Specifically, this study assessed the effects of: Gotukola plant materials of different genotypic origin; hexane, ethyl acetate and methanol extracts of Gotukola; and asiaticoside, a triterpenic compound isolated from Gotukola. Various paradigms were used to assess the anxiolytic activity, including the elevated plus maze (EPM), open field, social interaction, locomotor activity, punished drinking (Vogel) and novel cage tests. The EPM test revealed that Gotukola, its methanol and ethyl acetate extracts as well as the pure asiaticoside, imparted anxiolytic activity. Furthermore, the asiaticoside did not affect

locomotor activity, suggesting these compounds do not have sedative effects in rodents.
PMID: 16488124

Physiol Behav. 2005 Nov 15;86(4):449-57. Epub 2005 Oct 6.

Centella asiatica treatment during postnatal period enhances learning and memory in mice.

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Present investigation was planned to evaluate the nootropic effect of *Centella asiatica*. Three months old male Swiss albino mice were injected orally with graded doses (200, 500, 700, 1000 mg/kg body weight) of *C. asiatica* aqueous extract for 15 days to select an effective dose for nootropic studies. Animals were tested in radial arm maze to assess the learning and memory performance. Based on these results, mice were treated orally with 200 mg/kg of *C. asiatica* for 15 days from day 15 to day 30 post partum (p.p.) and the nootropic effect was evaluated on the 31st day and 6 months p.p. The behavioral (open field, dark/bright arena, hole board and radial arm maze tests), biochemical (acetylcholine esterase activity) and histological studies (dendritic arborization) were carried out. Performance of juvenile and young adult mice was significantly improved in radial arm maze and hole board tests, but locomotor activity did not show any change compared to control. Treatment resulted in increased acetylcholine esterase activity in the hippocampus. Dendritic arborization of hippocampal CA3 neurons was also increased in terms of intersections and branching points, both at one month and 6 months. Results of the present investigation show that treatment during postnatal developmental stage with *C. asiatica* extract can influence the neuronal morphology and promote the higher brain function of juvenile and young adult mice.

PMID: 16214185

Zhong Yao Cai. 2005 Jun;28(6):492-6.

[Effects of total triterpenes of *Centella asiatica* on the corticosterone levels in serum and contents of monoamine in depression rat brain][Article in Chinese]

Chen Y, Han T, Rui Y, Yin M, Qin L, Zheng H.

Pharmacy School, Shanghai Jiao Tong University, Shanghai.

OBJECTIVE: To investigate the possible antidepressant effect of total triterpenes of *Centella asiatica*. METHODS: The corticosterone levels in serum were measured by fluorescence spectroscopy. The contents of monoamine neurotransmitters and their metabolites in rats cortex, hippocampus and thalamus were evaluated by using HPLC with electrochemical detector. RESULTS: Significant reduction of the corticosterone level in serum and increase of the contents of 5-HT, NE, DA and their metabolites 5-HIAA, MHPG in rat brain were observed. CONCLUSION: The antidepressant effect of total triterpenes of *Centella asiatica* may be involved in ameliorating the function of HPA axis and increasing the contents of monoamine neurotransmitters. PMID: 16209267

Phytother Res. 2005 Jul;19(7):605-11.

Modification of gamma ray induced changes in the mouse hepatocytes by *Centella asiatica* extract: in vivo studies.

Sharma R, Sharma J.

Department of Zoology, University of Rajasthan, Jaipur 302004, India.

Ionizing radiation, besides causing direct damage also generates reactive oxygen species that are capable of inducing damage to various organs. Pretreatment with *Centella asiatica* 1 h prior to irradiation at a dose rate of 100 mg/kg body weight was found to be effective against radiation induced damage in the liver. The number of normal hepatocytes was higher in the *Centella asiatica* pretreated group in comparison with the irradiated only group. The number of binucleated cells and abnormal hepatocytes was less in comparison with the animals irradiated without *Centella asiatica* pretreatment. PMID: 16161023

J Pharm Pharmacol. 2005 Sep;57(9):1221-9.

Centella asiatica accelerates nerve regeneration upon oral administration and contains multiple active fractions increasing neurite elongation in-vitro.

Soumyanath A, Zhong YP, Gold SA, Yu X, Koop DR, Bourdette D, Gold BG.

Department of Neurology, Oregon Health & Science University, USA.

Axonal regeneration is important for functional recovery following nerve damage. *Centella asiatica* Urban herb, also known as *Hydrocotyle asiatica* L., has been used in Ayurvedic medicine for centuries as a nerve tonic. Here, we show that *Centella asiatica* ethanolic extract (100 microg mL⁻¹) elicits a marked increase in neurite outgrowth in human SH-SY5Y cells in the presence of nerve growth factor (NGF). However, a water extract of *Centella* was ineffective at 100 microg mL⁻¹. Sub-fractions of *Centella* ethanolic extract, obtained through silica-gel chromatography, were tested (100 microg mL⁻¹) for neurite elongation in the presence of NGF. Greatest activity was found with a non-polar fraction (GKF4). Relatively polar fractions (GKF10 to GKF13) also showed activity, albeit less than GKF4. Thus, *Centella* contains more than one active component. Asiatic acid (AA), a triterpenoid compound found in *Centella* ethanolic extract and GKF4, showed marked activity at 1 microM (microg mL⁻¹). AA was not present in GKF10 to GKF13, further indicating that other active components must be present. Neurite elongation by AA was completely blocked by the extracellular-signal-regulated kinase (ERK) pathway inhibitor PD 098059 (10 microM). Male Sprague-Dawley rats given *Centella* ethanolic extract in their drinking water (300-330 mg kg⁻¹ daily) demonstrated more rapid functional recovery and increased axonal regeneration (larger calibre axons and greater numbers of myelinated axons) compared with controls, indicating that the axons grew at a faster rate. Taken together, our findings indicate that components in *Centella* ethanolic extract may be useful for accelerating repair of damaged neurons. PMID: 16105244

Exp Gerontol. 2005 Aug-Sep;40(8-9):707-15.

Emerging role of Centella asiatica in improving age-related neurological antioxidant status.

Subathra M, Shila S, Devi MA, Panneerselvam C.

Department of Biochemistry, Dr AL Mudaliar PG Institute of Basic Medical Sciences, University of Madras, Taramani Campus, Chennai 600 113, India.

Free radicals have been hypothesized to play an important role in ageing process. There exists an imbalance between free radical production and antioxidant defense mechanism, which may lead to cell death during ageing. Our study was designed to determine whether extract of *Centella asiatica*, an antioxidant, when administered orally (300 mg/kg body weight/day) for 60 days would prevent age-related changes in antioxidant defense system, lipid peroxidation (LPO) and protein carbonyl (PCO) content in rat brain regions such as cortex, hypothalamus, striatum, cerebellum and hippocampus. Aged rats elicited a significant decline in the antioxidant status and increased the LPO and PCO as compared to control rats in all five regions studied. The increase in LPO and PCO contents were (64%, 34%) in cortex, (86%, 30%) in cerebellum, (51%, 47%) in striatum, (77%, 27%) in hypothalamus and (58%, 45%) in hippocampus, respectively, in aged rats as compared to young rats. Supplementation of *C. asiatica* was effective in reducing brain regional LPO and PCO levels and in increasing the antioxidant status. Thus, *C. asiatica* by acting as a potent antioxidant exerted significant neuroprotective effect and proved efficacious in protecting rat brain against age related oxidative damage.

PMID: 16026958

Phytomedicine. 2004;11(4):361-5.

Preliminary immunomodulatory activities of methanol extracts of *Eclipta alba* and *Centella asiatica*.

Jayathirtha MG, Mishra SH.

Pharmacy Department, The M.S. University of Baroda, Kalabhavan, Vadodara 390 001, India.

An attempt has been made to assess the immunomodulatory activity of methanol extracts of whole plant of *E. alba* (1.6% wedelolactone) and *C. asiatica* (0.18% of asiaticoside) at five dose levels (dose-response relationship) ranging from 100 to 500 mg/kg body wt. using carbon clearance, antibody titer and cyclophosphamide immunosuppression parameters. In the case of *E. alba*, the phagocytic index and antibody titer increased significantly and the F ratios of the phagocytic index and WBC count were also significant. Regression analysis showed linearity in patterns of the dose-response relationship, greatest in the case of the phagocytic index, moderate in the WBC count and lowest in the antibody titer. For *C. asiatica*, significant increases in the phagocytic index and total WBC count were observed and the F ratio of the phagocytic index was also significant. Regressed values revealed maximum linearity in the case of the phagocytic index, moderate linearity in the total WBC count and lowest linearity in the antibody response. PMID: 15185851

J Ethnopharmacol. 2004 Jul;93(1):105-8.

Cardioprotective activity of *Hydrocotyle asiatica* L. in ischemia-reperfusion induced myocardial infarction in rats.

Pragada RR, Veeravalli KK, Chowdary KP, Routhu KV.

Pharmacology Division, Department of Pharmaceutical Sciences, Andhra University, India.

The alcoholic extract of *Hydrocotyle asiatica* Linn. (*Hydrocotyle asiatica* L.) whole plant was evaluated for cardioprotective activity against ischemia-reperfusion induced myocardial infarction in rats. Cardioprotective activity was studied by measuring infarct size and estimating lipid peroxide levels in serum and heart tissue. A lead II electrocardiogram was monitored at various intervals throughout the experiment. A dose (100-1000 mg kg⁻¹) dependent reduction in percent left ventricle necrosis (PLVN) as well as in lipid peroxide levels was observed in rats treated with alcoholic extract of *Hydrocotyle asiatica* L. orally for 7 days compared to control animals. The study strongly suggests the cardioprotective activity of *Hydrocotyle asiatica* L. in limiting ischemia-reperfusion induced myocardial injury. PMID: 15182913

Zhong Yao Cai. 2003 Dec;26(12):870-3.

[Effect of total triterpenes from *Centella asiatica* on the depression behavior and concentration of amino acid in forced swimming mice][Article in Chinese]

Chen Y, Han T, Qin L, Rui Y, Zheng H.

School of Pharmacy, Second Military Medical University, Shanghai 200433.

OBJECTIVE: To evaluate the antidepressant activity of total triterpenes from *Centella asiatica* in forced swimming test. METHODS: Mice were randomly divided into control group, model group and treatment group. The effect of total triterpenes from *Centella asiatica* on the immobility time in forced swimming mice and concentration of amino acid in mice brain tissue was observed. RESULTS: Imipramine and total triterpenes from *Centella asiatica* reduced the immobility time and ameliorated the imbalance of amino acid levels. CONCLUSION: The total triterpenes from *Centella asiatica* had antidepressant activity. PMID: 15058206

Life Sci. 2004 Mar 19;74(18):2237-49.

The healing effects of Centella extract and asiaticoside on acetic acid induced gastric ulcers in rats.

Cheng CL, Guo JS, Luk J, Koo MW.

Department of Pharmacology, Faculty of Medicine, The University of Hong Kong, China.

In this study, the healing effects of *Centella asiatica* water extract (CE) and asiaticoside (AC), an active constituent of CE, on acetic acid induced gastric ulcers (kissing ulcers) in rats were examined. CE was prepared from *Centella asiatica* dry plant and the concentration of AC in CE was quantitatively determined with the use of high performance liquid chromatography analysis. Different concentrations of CE and AC were orally administered to rats with kissing ulcers. They were found to reduce the size of the ulcers at day 3 and 7 in a dose-dependent manner, with a concomitant attenuation of myeloperoxidase activity at the ulcer tissues. Epithelial cell proliferation and angiogenesis were on the other hand promoted. The expression of basic fibroblast growth factor, an important angiogenic factor, was also upregulated in the ulcer tissues in rats treated with CE or AC. These results further suggest the potential use of *Centella asiatica* and its active ingredient as anti-gastric ulcers drugs. PMID: 14987949

Clin Exp Pharmacol Physiol. 2003 May-Jun;30(5-6):336-42.

Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats.

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1. *Centella asiatica*, an Indian medicinal plant, has been described as possessing central nervous system activity, such as improving intelligence. In addition, we have demonstrated that *C. asiatica* has cognitive-enhancing and anti-oxidant properties in normal rats. Oxidative stress or an impaired endogenous anti-oxidant mechanism is an important factor that has been implicated in Alzheimer's disease (AD) and cognitive deficits seen in the elderly. 2. Intracerebroventricular (i.c.v.) streptozotocin (STZ) in rats has been likened to sporadic AD in humans and the cognitive impairment is associated with free radical generation in this model. Therefore, in the present study, the effect of an aqueous extract of *C. asiatica* (100, 200 and 300 mg/kg for 21 days) was evaluated in i.c.v. STZ-induced cognitive impairment and oxidative stress in rats. 3. Male Wistar rats were injected with STZ (3 mg/kg, i.c.v.) bilaterally on the days 1 and 3. Cognitive behaviour was assessed using passive avoidance and elevated plus-maze paradigms on the days 13, 14 and 21. Rats were killed on the day 21 for estimation of oxidative stress parameters (malondialdehyde (MDA), glutathione, superoxide dismutase and catalase) in the whole brain upon completion of the behavioural task. 4. Rats treated with *C. asiatica* showed a dose-dependent increase in cognitive behaviour in both 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 *C. asiatica*. 5. The present findings indicate that an aqueous extract of *C. asiatica* is effective in preventing the cognitive deficits, as well as the oxidative stress, caused by i.c.v. STZ in rats. PMID: 12859423

Fitoterapia. 2003 Jul;74(5):431-4.

Anti-oxidant activity of Centella asiatica on lymphoma-bearing mice.

Jayashree G, Kurup Muraleedhara G, Sudarslal S, Jacob VB.

Applied Biochemistry Laboratory, School of Biosciences, MG University, India.

Oral treatment with 50 mg X kg⁻¹ day⁻¹ of crude methanol extract of *Centella asiatica* for 14 days significantly increased the anti-oxidant enzymes, like superoxide dismutase (SOD), catalase and glutathione peroxidase (GSHPx), and anti-oxidants like glutathione (GSH) and ascorbic acid decreased in lymphoma-bearing mice. PMID: 12837356

Pharmacol Biochem Behav. 2003 Feb;74(3):579-85.

Effect of Centella asiatica on pentylenetetrazole-induced kindling, cognition and oxidative stress in rats.

Gupta YK, Veerendra Kumar MH, Srivastava AK.

Neuropharmacology Laboratory, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India.

Cognitive impairment in epileptics may be a consequence of the epileptogenic process as well as antiepileptic medication. Thus, there is a need for drugs, which can suppress epileptogenesis as well as prevent cognitive impairment. In the present study, the effect of aqueous extract of *Centella asiatica* (CA) (100 and 300 mg/kg), an Indian medicinal plant known to possess antiepileptic, cognitive-enhancing and antioxidant property, was evaluated on the course of kindling development, kindling-induced learning deficit and oxidative stress markers in pentylenetetrazole (PTZ) kindled rats. Male Wistar rats were injected PTZ (30 mg/kg ip) once every alternate day (48 \pm 2 h) until the development of the kindling. Passive avoidance test and spontaneous locomotor activity were carried out 24 and 48 h after the last administration of PTZ, while the oxidative stress parameters (malondialdehyde [MDA] and glutathione) were carried out in the whole brain upon completion of the behavioral assessment. The administration of CA (300 mg/kg orally) 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 behavior. However, low dose of the CA (100 mg/kg) showed improvement only in the learning deficit due to the kindling and failed to improve the seizure score. The findings suggest the potential of aqueous extract of CA as adjuvant to antiepileptic drugs with an added advantage of preventing cognitive impairment.

PMID: 12543222

Phytother Res. 2002 Dec;16(8):785-6.

Radioprotection of Swiss albino mouse by Centella asiatica extract.

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Department of Zoology, University of Rajasthan, Jaipur 302004, India.

Centella asiatica, has a considerable reputation in the Indian system of medicine. It is a rasayan (general tonic), brain tonic, improves memory and strengthens the CNS. In view of its multifarious uses, the plant extract was tested for its radioprotective properties. A sublethal dose of Co 60 gamma radiation, i.e. 8 Gy was selected for the purpose. Animals were divided into two groups. The whole bodies were irradiated with Co 60 gamma radiation externally, with and without drug extract. The drug extract was given orally at different doses and for different time intervals. The dose that was most effective against radiation was 100 mg/kg body weight. This 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. The causes and mechanism of protection and other aspects need further investigations. Copyright 2002 John Wiley & Sons, Ltd. PMID: 12458490

J Ethnopharmacol. 2002 Feb;79(2):253-60.

Effect of different extracts of Centella asiatica on cognition and markers of oxidative stress in rats.

Veerendra Kumar MH, Gupta YK.

Department of Pharmacology, Neuropharmacology Laboratory, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

Centella asiatica, a plant mentioned in Indian literature has been described to possess CNS effects such as stimulatory-nervine tonic, rejuvenant, sedative, tranquilizer and intelligence promoting property. In the present study aqueous, methanolic and chloroform extracts of C.

asiatica were investigated for their effect on cognitive functions in rats. Male Wistar rats of 200-250 g were used to study the effect on learning and memory by using shuttle box, step through, step down and elevated plus maze paradigms. Only the aqueous extract of whole plant (200 mg/kg for 14 days) showed an improvement in learning and memory in both shuttle box and step through paradigms. Therefore, further experiments were conducted with aqueous extract using 100, 200 and 300 mg/kg doses in different paradigms of learning and memory. All doses of aqueous extract increased the number of avoidances in shuttle box and prolonged the step through latency in step through apparatus in a dose dependent manner, while only two doses 200 and 300 mg/kg of aqueous extract showed significant increase in the step down latency in step down apparatus and transfer latency (TL) in elevated plus maze. Among doses of aqueous extract tested on oxidative stress parameters, only 200 and 300 mg/kg showed a significant decrease in the brain levels of malondialdehyde (MDA) with simultaneous significant increase in levels of glutathione. There was a significant increase in the levels of catalase at the 300 mg/kg but no significant change in superoxide dismutase (SOD) levels were observed. The present findings indicate that the aqueous extract of *C. asiatica* has cognitive enhancing effect and an antioxidant mechanism is involved. PMID: 11801389

Res Commun Mol Pathol Pharmacol. 2000 Jul-Aug;108(1-2):75-86.

Asiatic acid derivatives protect cultured cortical neurons from glutamate-induced excitotoxicity.

Lee MK, Kim SR, Sung SH, Lim D, Kim H, Choi H, Park HK, Je S, Ki YC.

College of Pharmacy, Seoul National University, Korea.

Asiatic acid, a triterpene of *Centella asiatica* (L.) Urban (Umbelliferae), has been patented as a treatment for dementia and an enhancer of cognition by the Hoechst Aktiengesellschaft (EP 0 383 171 A2). We modified the chemical structure of asiatic acid and obtained 36 derivatives of asiatic acid in an attempt to prepare neuroprotective compounds that were more efficacious than asiatic acid itself. The neuroprotective activities of these derivatives were evaluated using primary cultures of rat cortical neurons insulted with the neurotoxin, glutamate, as an in vitro screening system. Among the semi-synthesized derivatives, three derivatives significantly mitigated the neurotoxicity induced by glutamate in this screening system. The neuroprotective activities of these 3 derivatives appeared to be more powerful than that of asiatic acid itself. These 3 derivatives significantly attenuated decreases in the levels of glutathione, glutathione peroxidase and other enzymes, which participate in the cellular defense mechanisms blunting oxidative stress. Furthermore, they significantly reduced the overproduction of NO induced by glutamate. These results showed that these derivatives of asiatic acid exerted significant neuroprotective effects on cultured cortical cells by their potentiation of the cellular oxidative defense mechanism. Therefore, these agents may prove to be efficacious in protecting neurons from the oxidative damage caused by exposure to excess glutamate. PMID: 11758977

Natural Medicine, July/August 1996, Vol. 3, No. 6, pp. 22-25, American Botanical Council, February 5, 1997 HC 020571

Gotu Kola (*Centella asiatica*) Monograph

Anonymous. *Centella asiatica* (Gotu kola). Gotu kola (*Centella asiatica*) has been used traditionally as a medicine in India and Indonesia, primarily for its wound healing properties and its ability to relieve leprosy. In a nineteenth century Indian pharmacopeia, it was listed as treatment for skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis, and wounds. It was also used to treat diarrhea, fever, amenorrhea [absence of menses], and female genito-urinary tract diseases. The leaves, shoots and whole plant have also been used medicinally in China. Gotu kola's constituents of primary pharmacological interest are its triterpenoids, which have been shown to exert a complex set of actions on cells and tissues, particularly connective tissues, participating in the healing process. The herb's

clinical applications include treatment of second and third degree burns, cellulite, cirrhosis of the liver, keloids [sharply elevated, irregularly shaped, progressively enlarging scar due to excessive collagen formation] and hypertrophic [enlarged] scars, leprosy, scleroderma [chronic hardening or shrinkage of the connective tissue], varicose veins and venous insufficiency, and wound repair. Gotu kola has also been shown in a clinical trial to significantly increase mental function, demonstrating a mild tranquilizing and anti-anxiety action.

Proprietary formulas of gotu kola are standardized to contain asiaticosides (40%), asiatic acid (29 to 30%), madecassic acid (29-30%), and madecassoside (1-2%). These are available in both Europe and the US, and should be taken at a dosage of 60 to 120 mg a day. Gotu kola is well tolerated orally; topical application has led to infrequent cases of contact dermatitis.

Angiology 2001 Oct;52 Suppl 2:S9-13

Total triterpenic fraction of Centella asiatica in chronic venous insufficiency and in high-perfusion microangiopathy.

Incandela L, Cesarone MR, Cacchio M, De Sanctis MT, Santavenere C, D'Auro MG et al.
Vascular Unit, Ealing Hospital, London, UK.
Total triterpenic fraction of Centella asiatica (TTFCA) is effective in improving venous wall alterations in chronic venous hypertension and in protecting the venous endothelium. TTFCA is active on connective tissue modulation, improves the synthesis of collagen and other tissue proteins by modulating the action of fibroblasts in the vein wall, and stimulates collagen remodeling in and around the venous wall. This is due to the modulating action of TTFCA on fibroblasts as shown by experiments on the growth of human embryonal fibroblasts. TTFCA has a moderate in-vitro and in-vivo stimulating effect on collagen synthesis and, at higher dosages, an inhibition on the synthesis of collagen and acid mucopolysaccharides. Studies have indicated the role of TTFCA on the synthesis of specific venous wall elements by cell cultures of human embryonal fibroblasts. The tissue-stimulating action is shown by the increased collagen production independent from the stimulation of cell proliferation (this differentiates the action of TTFCA from cell growth factors). TTFCA is active on the microcirculation in venous and diabetic microangiopathy. Signs and symptoms of venous hypertension and edema are improved by treatment. The remodeling on collagen synthesis could be one of the possible mechanisms of actions of TTFCA in the remodeling of echolucent (soft; therefore, with risk of thrombosis and embolization) plaques at the carotid and femoral bifurcation. This compound is safe and well tolerated. In conclusion, several actions of TTFCA in vascular diseases makes the use of this compound very interesting in venous and arterial problems. PMID: 11666128

Angiology 2001 Oct;52 Suppl 2:S61-7

Total triterpenic fraction of Centella asiatica in the treatment of venous hypertension: a clinical, prospective, randomized trial using a combined microcirculatory model.

Incandela L, Belcaro G, De Sanctis MT, Cesarone MR, Griffin M, Ippolito E et al.
Irvine Vascular Laboratory, St Mary's Hospital and Imperial College, London, UK.
A single-blind, placebo-controlled, randomized study was performed on the effects of different doses of the total triterpenic fraction of Centella asiatica (TTFCA) in patients with venous hypertensive microangiopathy. A combined microcirculatory model that considers laser Doppler flowmetry (LDF) and transcutaneous oxygen (PO₂), transcutaneous carbon dioxide tension (PCO₂) measurements was combined with the symptom evaluation. LDF tests included the baseline resting flow, the venoarteriolar reflex, and the variation of flow related to the temperature increase. All tests provided a significant difference between drug-treated groups and the placebo group, thereby allowing a distinction to be made between the higher (120 mg daily) and the lower (60 mg daily) dose of TTFCA.

Transcutaneous PO₂-PCO₂ measurements were significantly modified by drug treatments, while no variation could be detected in the placebo group. Important symptomatologic effects (evaluated by subjective scores) followed TTFCA administration, especially at the higher dose level, while no effect was obtained with placebo. The trend of symptom evaluation paralleled the results of objective tests of our microcirculatory model, providing evidence that this model can reveal effects of venoactive drugs on venous hypertensive microangiopathy. TTFCA displays a significant activity. Doses as high as 120 mg daily may be safely used in venous hypertension. PMID: 11666126

Altern Med Rev 2001 Apr;6(2):126-40

Hemorrhoids and varicose veins: a review of treatment options.
Mackay *D.*

Thorne Research, 4616 SE 30th, Portland, OR 97202, USA. Hemorrhoids and varicose veins are common conditions seen by general practitioners. Both conditions have several treatment modalities for the physician to choose from. Varicose veins are treated with mechanical compression stockings. There are several over-the-counter topical agents available for hemorrhoids. Conservative therapies for both conditions include diet, lifestyle changes, and hydrotherapy which require a high degree of patient compliance to be effective. When conservative hemorrhoid therapy is ineffective, many physicians may choose other non-surgical modalities: injection sclerotherapy, cryotherapy, manual dilation of the anus, infrared photocoagulation, bipolar diathermy, direct current electrocoagulation, or rubber band ligation. Injection sclerotherapy is the non-surgical treatment for primary varicose veins. Non-surgical modalities require physicians to be specially trained, own specialized equipment, and assume associated risks. If a non-surgical approach fails, the patient is often referred to a surgeon. The costly and uncomfortable nature of treatment options often lead a patient to postpone evaluation until aggressive intervention is necessary. Oral dietary supplementation is an attractive addition to the traditional treatment of hemorrhoids and varicose veins. The loss of vascular integrity is associated with the pathogenesis of both hemorrhoids and varicose veins. Several botanical extracts have been shown to improve microcirculation, capillary flow, and vascular tone, and to strengthen the connective tissue of the perivascular amorphous substrate. Oral supplementation with *Aesculus hippocastanum*, *Ruscus aculeatus*, *Centella asiatica*, *Hamamelis virginiana*, and bioflavonoids may prevent time-consuming, painful, and expensive complications of varicose veins and hemorrhoids.

Minerva Cardioangiol 2001 Apr;49(2):159-63

[Effectiveness of the combination of alpha tocopherol, rutin, melilotus, and centella asiatica in the treatment of patients with chronic venous insufficiency][Article in Italian]

Cataldi A, Gasbarro V, Viaggi R, Soverini R, Gresta E, Mascoli F.
Unita Operativa Chirurgia Vascolare, Arcispedale S. Anna, Turin, Italy.
BACKGROUND: The aim of this comparative clinical study was to evaluate the efficacy of the association of alphas-tocopherol, rutin, melilotus officinalis, and centella asiatica with oral administration in patients with chronic venous insufficiency. METHODS: Thirty patients with chronic venous insufficiency have been randomized in two groups of fifteen subjects (control and treatment group). During the period of treatment the patients didn't wear elastocompressive stockings. The therapeutic efficacy and the clinical tolerability of this association have been valued with clinical-instrumental evaluations and by a control after 15 and 30 days. Functional bothers, cramps and the edema have been valued in function presence and of their gravity with a clinical-score between 0 and 4. RESULTS: At the end of the observation period, a significant improvement of the clinical symptomatology was obtained, characterised by a diminution of the sovrafascial edema. CONCLUSIONS: The present study confirms previous clinical experiences regarding the described treatment and

suggests its application in chronic venous insufficiency.
PMID: 11292962

Phytother Res 1999 Feb;13(1):50-4

Asiaticoside-induced elevation of antioxidant levels in healing wounds.

Shukla A, Rasik AM, Dhawan BN

Pharmacology Department, Central Drug Research Institute, Lucknow, India.

Asiaticoside derived from the plant *Centella asiatica* is known to possess good wound healing activity. Enhanced healing activity has been attributed to increased collagen formation and angiogenesis. Since antioxidants have been reported to play a significant role in the wound healing process we studied the effect of asiaticoside on the levels of certain antioxidants in the wound so as to explore the possible involvement of such a mechanism in the asiaticoside induced wound healing. Asiaticoside application (0.2%, topical) twice daily for 7 days to excision-type cutaneous wounds in rats led to increased enzymatic and non-enzymatic antioxidants, namely superoxide dismutase (35%), catalase (67%), glutathione peroxidase (49%), vitamin E (77%) and ascorbic acid (36%) in newly formed tissues. It also resulted in a several fold decrease in lipid peroxide levels (69%) as measured in terms of thiobarbituric acid reactive substance. However, continued application for 14 days showed no significant difference in these antioxidants compared with their values in vehicle treated wound tissue. It appears from the present study that asiaticosides enhanced induction of antioxidant levels at an initial stage of healing which may be an important contributory factor in the healing properties of this substance. PMID: 10189951, UI: 99205949

J Chromatogr Sci 1999 Feb;37(2):51-5

Extraction and analysis of cosmetic active ingredients from an anti-cellulitis transdermal delivery system by high-performance liquid chromatography.

Morganti P, Fionda A, Elia U, Tiberi L

Mavi Sud, Research & Development Laboratories, Aprilia, Italy.

A new transdermal delivery system that controls cellulitis is evaluated using reversed-phase high-performance liquid chromatography coupled with photodiode array detection. An extraction procedure and the validation of the analytical method to assay the active excipients from the *Centella asiatica* plant (asiaticoside, madacessic acid, and asiatic acid) are described. Excellent results are obtained in terms of linearity, accuracy, and specificity of the analytical method.

PMID: 10065405, UI: 99164799

Indian J Exp Biol 1998 Jun;36(6):569-72

Evaluation of topical formulations of aqueous extract of *Centella asiatica* on open wounds in rats.

Sunilkumar, Parameshwaraiah S, Shivakumar HG

J.S.S. College of Pharmacy, Mysore, India.

Formulations (ointment, cream and gel) of aqueous extract of *C. asiatica*, when applied topically, thrice daily for 24 days on the open wounds in rats increased cellular proliferation and collagen synthesis at the wound site, as evidenced by increase in collagen content and tensile strength. The treated wounds epithelialised faster and the rate of wound contraction was higher as compared to control wounds. The process of healing was better with gel formulation when compared to other two formulations. PMID: 9731470, UI: 98401657

Indian J Exp Biol 1996 Dec;34(12):1208-11

Effects of *Centella asiatica* extract on dermal wound healing in rats.

Suguna L, Sivakumar P, Chandrakasan G

Department of Biochemistry, Central Leather Research Institute Madras, India.

Effects of oral and topical administration of an alcoholic extract of *C. asiatica* on rat dermal wound healing was studied. 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 crosslinking 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 epithelialise faster and the rate of wound contraction was higher, as compared to control wounds. The results show that *C. asiatica* produced different actions on the various phases of wound repair. PMID: 9246912

Minerva Cardioangiol 1994 Jun;42(6):299-304

[The microcirculatory activity of Centella asiatica in venous insufficiency. A double-blind study]. [Article in Italian]

Cesarone MR, Laurora G, De Sanctis MT, Incandela L, Grimaldi R, Marelli C, Belcaro G
Istituto di Clinica Cardiovascolare, Universita degli Studi G. D'Annunzio, Chieti.

In 87 patients with chronic venous hypertensive microangiopathy the efficacy of oral FTTCa (*Centella asiatica*) administered for 60 days was tested. The microcirculatory effects of two dosages (30 mg bid and 60 mg bid) versus placebo was assessed in a double blind study. The compound was well tolerated and no unwanted effects were observed. Microcirculatory parameters--peri-malleolar skin flux at rest (RF) and transcutaneous PO₂ and PCO₂--improved as did the abnormally increased RF, PCO₂ decreased and PO₂ increased in comparison with values measured at inclusion. These results confirm the efficacy of FTTCa in venous hypertensive microangiopathy. Furthermore the effects of FTTCa appear to be dose-related.

PMID: 7936334, UI: 95022298

Cytotechnology 1993;13(3):221-6

Enhancement of the attachment on microcarriers and tPA production by fibroblast cells in a serum-free medium by the addition of the extracts of Centella asiatica.

Kim YN, Park YS, Kim HK, Jeon BC, Youn SE, Lee HY

Department of Food Engineering, Kangwon National University, Chunchon, Korea.

The addition of ethanol extracts of *Centella asiatica* showed a remarkable enhancement of fibroblast cells attachment to Cytodex beads in serum-free (SF) medium. It also improves tPA production in both batch and perfusion cultivations. The optimal concentration for SF medium was determined as 2 ppm of the extracts when using Cytodex III. In batch cultivation a high specific tPA production rate was obtained, compared to that from 5% FBS containing medium. However, a fast specific growth rate was observed in 5% FBS medium. In perfusion cultivation a reasonably good cell density and tPA production was achieved at a perfusion rate of 2.4×10^6 (viable cell/ml) and 0.65 (micrograms/ml), respectively at 22 ml/min. PMID: 7764663

Minerva Cardioangiol 1992 Apr;40(4):137-43

[Activity of Centella asiatica in venous insufficiency]. [Article in Italian]

Cesarone MR, Laurora G, De Sanctis MT, Belcaro G

Clinica Cardiovascolare, Universita degli Studi G. D'Annunzio, Chieti.

In this a review concerning TTFCA, its effects on metabolism in the connective tissue of the vascular wall and on the microcirculation are presented and discussed. This compound is effective in venous insufficiency, reducing ankle edema, foot swelling, capillary filtration rate and by improving microcirculatory parameters (RF, VAR PO₂-PCO₂). TTFCA displays a significant activity in venous hypertensive microangiopathy and its effects are dose-dependent.

PMID: 1528498, UI: 92409085

Angiology 1990 Jul;41(7):533-40

Improvement of capillary permeability in patients with venous hypertension after treatment with TTFCA.

Belcaro GV, Grimaldi R, Guidi G

Microcirculation Laboratory, G. D'Annunzio University, Chieti, Italy.

The VSC (vacuum suction chamber) device, a new system to evaluate local capillary permeability, was used with laser Doppler flowmetry to study variations of permeability and of the microcirculation in 10 normal subjects; in 22 patients with moderate, superficial venous hypertension; and in 12 patients with postphlebotic limbs and severe venous hypertension. All these patients had distal (ankle and foot edema) in the evening. After a first assessment these subjects were studied again after two weeks without treatment and after two weeks' treatment with total triterpenic fraction of centella asiatica (TTFCA), tablets, 60 mg, tid. The VSC produces a wheal on the skin of the perimalleolar region that disappears (in average) in less than sixty minutes in normal subjects. The disappearance time (DT) is greater in conditions of increased capillary filtration and permeability. The three groups of subjects (normal and those with superficial and severe venous hypertension) had significantly different, increasing disappearance time of the wheals at the first observation. There were no significant changes after two weeks' observation, but after 2 weeks' treatment with TTFCA, there was a significant decrease of DT both in limbs with superficial and with deep venous incompetence. The improvement (decrease) of the abnormally increased capillary permeability was associated with a significant improvement of the microcirculation and symptoms (studied by an analogue scale line). In conclusion this study showed a combined improvement of the microcirculation and capillary permeability after treatment with TTFCA and the possibility of using the VSC to evaluate the effects of drugs (or other treatment) on local capillary permeability in patients with venous hypertension. PMID: 2389834, UI: 90358335

Connect Tissue Res 1990;24(2):107-20

Stimulation of collagen synthesis in fibroblast cultures by a triterpene extracted from Centella asiatica.

Maquart FX, Bellon G, Gillery P, Wegrowski Y, Borel JP

Laboratory of Biochemistry, CNRS URA, Faculty of Medicine, Reims, France.

The drug "Titrated Extract from Centella asiatica" (TECA), used for its stimulating properties on the healing of wounds, is a mixture of 3 terpenes extracted from a tropical plant: asiatic acid (30%, w/w), madecassic acid (30%, w/w) and asiaticoside (40%, w/w). The effects of TECA and its individual components were checked on human foreskin fibroblast monolayer cultures. TECA increased the collagen synthesis in a dose-dependent fashion whereas a simultaneous decrease in the specific activity of neosynthesized collagen was observed. Asiatic acid was found to be the only component responsible for collagen synthesis stimulation. TECA and all three terpenes increased the intracellular free proline pool. This effect was independent of the stimulation of collagen synthesis. PMID: 2354631, UI: 90284242

Angiology 1990 Jan;41(1):12-8

Capillary filtration and ankle edema in patients with venous hypertension treated with TTFCA.

Belcaro GV, Rulo A, Grimaldi R

Cardiovascular Clinic, University G. D'Annunzio, Chieti, Italy.

The variation of capillary filtration rate (CFR), ankle circumference (AC), and ankle edema (AE) was evaluated in three groups of patients with venous hypertension (ambulatory venous pressure greater than 42 mmHg) and in a group of normal subjects before and after treatment for four weeks with Total Triterpenic fraction of Centella Asiatica (TTFCA), a venoactive drug acting on the microcirculation and on capillary permeability. Group A (20

patients) was treated with TTFCA 60 mg tid; Group B (20 patients) was treated with 30 mg tid; Group C (12 patients) was treated with placebo; and Group D (10 normal subjects) was treated with TTFCA 60 mg tid in an open study. Capillary filtration rate was assessed by venous occlusion plethysmography, ankle edema by a new system called AECT (Ankle edema coin tester). Subjective symptoms of venous hypertension were assessed by an analogue scale line considering four symptoms: swelling sensation, restless lower extremity, pain and cramps, and tiredness. CFR, AC, and AE were significantly higher in patients in comparison with normal subjects. After four weeks of TTFCA treatment there was a significant decrease of the abnormally increased CFR, AC, and AECT time in patients. This was also greater in the higher dose group. No significant change was observed in the placebo group and in normal subjects treated with TTFCA. Symptoms were also significantly improved in the two groups treated with the active drug according to the dose. No significant changes were observed in the placebo group. PMID: 2305995, UI: 90165001

Int J Clin Pharmacol Res 1990;10(4):229-33

Effects of Centella asiatica extract on mucopolysaccharide metabolism in subjects with varicose veins.

Arpaia MR, Ferrone R, Amitrano M, Nappo C, Leonardo G, del Guercio R

The effects were studied of the total triterpenic fraction of *Centella asiatica* on serum levels of the uronic acids and lysosomal enzymes involved in mucopolysaccharide metabolism (beta-glycuronidase, beta-N-acetylglucosaminidase, arylsulfatase) in patients with varicose veins. The basal levels of uronic acids (467.7 +/- 69.3 micrograms/ml) and of lysosomal enzymes (beta-glycuronidase 1.8 +/- 0.4 microM/min/l, beta-N-acetylglucosaminidase 23.1 +/- 0.4 microM/min/l, arylsulfatase 0.078 +/- 0.003 microM/min/l) were elevated, indicating an increased mucopolysaccharide turnover in subjects with varicose veins. During treatment with *Centella asiatica* extract (60 mg/day for three months), these levels fell progressively. At the end of treatment the serum uronic acid (231.8 +/- 51.5 micrograms/ml), beta-glycuronidase (1.2 +/- 0.05 microM/min/l), beta-N-acetylglucosaminidase (17.7 +/- 0.7 microM/min/l) and arylsulfatase (0.042 +/- 0.003 microM/min/l) levels were highly significantly lower than the basal levels (p less than 0.01). The results of this trial provide an indirect confirmation of regulatory effects of the extract of *Centella asiatica* on metabolism in the connective tissue of the vascular wall.

PMID: 2150405, UI: 91177616

Ital J Biochem 1988 Mar-Apr;37(2):69-77

Effect of the triterpenoid fraction of Centella asiatica on macromolecules of the connective matrix in human skin fibroblast cultures.

Tenni R, Zanaboni G, De Agostini MP, Rossi A, Bendotti C, Cetta G

Dipartimento di Biochimica, Universita di Pavia.

The mechanism of action of the total triterpenoid fraction extracted from *Centella Asiatica* (TTFCA) was evaluated using human skin fibroblasts cultures as the experimental system. In particular its influence on the biosynthesis of collagen, fibronectin and proteoglycans was considered. The presence of TTFCA (25 micrograms/ml) does not seem to affect cell proliferation, total protein synthesis or the biosynthesis of proteoglycans in a significant way. A statistically important increase was observed in the percentage of collagen and, as revealed by immunofluorescence measurements, in cell layer fibronectin. This effect on collagen and fibronectin may help to explain the action of TTFCA in promoting wound healing, and suggests an interesting working hypothesis for its action on basal endothelia.

PMID: 3042688

Angiology 1987 Jan;38(1 Pt 1):46-50

Titrated extract of Centella asiatica (TECA) in the treatment of venous insufficiency of the lower limbs.

Pointel JP, Boccalon H, Cloarec M, Ledevhat C, Joubert M

Ninety-four patients suffering from venous insufficiency of the lower limbs participated in a multicenter, double-blind versus placebo study. After randomization, they were allotted for a treatment period of two months to one of three groups: TECA 120 mg/day, TECA 60 mg/day, or placebo. A significant difference (p less than 0.05) in favor of TECA was shown for the symptoms of heaviness in the lower limbs and edema, as well as for the overall evaluation by the patient. The venous distensibility measured by a mercury strain gauge plethysmograph at three occlusion pressures was improved for the TECA groups but aggravated for the placebo group. PMID: 3544968, UI: 87125970