IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review on Theurapeutic Properties of *Centella asiatica* and Furture Perspectives

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Abstract: Plant-based drug discovery has drawn the attention of researchers, especially the one used as traditional medicines. Centella asiatica, a medicinal herb widely distributed throughout the world is popular as a traditional medicine. In Ayurveda, it is used either alone or as an important ingredient of several formulations for the management of CNS, skin and gastrointestinal diseases. The aerial parts and roots are used for medicinal purpose, and its chemical constituents have wide therapeutic applications in areas of antimicrobial, anti-inflammatory, anticancer, neuroprotective, antioxidant, and wound healing activities. Many of its uses have been proven scientifically, and bioactive ingredients have been validated. Hence, in this narrative review of literature study we aimed to describe and delineate the therapeutic properties of Centella asiatica and overview on future perspectives are also highlighted.

Keywords - *Centella asiatica*, Ayurveda, Traditional medicine, Anti-inflammatory, Anticancer, Neuroprotective

I. INTRODUCTION

Centella asiatica (L) urban, synonym Hydrocotyle asiatica, belongs to the family Apiaceae (Umbelliferae). This herb is found almost all over the world, particularly during rainy season and in damp and marshy areas. It is a popular medicinal plant in several traditional systems of medicine. In Ayurveda, an Indian system of medicine, this is an important ingredient of several compound formulations used in the management of central nervous system, skin and gastrointestinal disorders (Sharma, 1981).

It is also used alone and has been considered by Vagbhatt as the best herb for improving memory and intellect. It belongs to the group of drugs known as medhya rasayanas (psychotropic drugs) and is also known as Brahmi. The literal, meaning of the term, Brahmi is one which promotes the intellect and that is why many herbs with similar effects are known as Brahmi. This has led to the popular controversy associated with this herb, as presently two herbs, *viz. Centella asiatica* and *Bacopa monnieri*, are used by the same name of Brahmi in different parts of India. To avoid the confusion, it has been suggested to refer this plant by its other name mandukaparni, a synonym indicating towards its peculiar leaves (Sharma, 1981). In English this is known as waternavel, waterpennywort and Indianpennywort.

II. BOTANICAL OF DESCRIPTION OF *CENTELLA ASIATICA*

Centella asiatica is a slender trailing herb, rooting at the nodes. It has long, reddish, prostate stem emerging from the leaf axils of a vertical root stock. Leaves are orbicular, reniform, entire, crenate, glaborous, 1.3-7 cm in diameter. Flowers are sessile, white or reddish, covered by bracts and 3-6 flowers are arranged in an umbel. Fruits are small, compressed, 8 mm long, mericarps are curved, rounded at the top, broad and 7-9 ridged. Seeds are compressed laterally. This has a characteristic odour, greyish green colour and bittersweet taste (Figure 1) (Arora et al 2002).

Figure 1: Showing whole plant, flowers, seeds and fruit parts of *Centella asiatica*

With regards of habitat of *Centella asiatica*, the plant is an indigenous to the warmer regions of both the hemispheres, including Asia, Africa, Australia, southern United States of America, Central America and South America. It is especially abundant in the swampy areas of India, up to an altitude of approximately 700 m. It is abundantly found during rainy season (Arora et al 2002).

Taxonomy of *Centella asiatica*

Kingdom Plantae – Plants

Subkingdom Tracheobionta – Vascular plants

Superdivision Spermatophyta – Seed plants

Division Magnoliophyta – Flowering plants

Class Magnoliopsida – Dicotyledons

Subclass Rosidae

Order Apiales

Family Apiaceae – Carrot family

Genus *Centella* L. – centella

Species *Centella asiatica* (L.) Urb. – spadeleaf (USDA 2021)

III. NUTRIENT COMPOSITION OF *CENTELLA ASIATICA*

Generally, Centella asiatica are rich sources of minerals (including iron, calcium, potassium, and magnesium) and vitamins, including vitamins K, C, E, and many of the B vitamins. They also provide a variety of phytonutrients including β-carotene, lutein, neoxanthin, and zeaxanthin, which protect human cells from damages and eyes from age-related problems among many other effects. Macronutrients found in *Centella asiatica* are mainly proteins, carbohydrates, and fibers. According to three studies done in the previous decade, the content of nutrients shows relatively close values but in some instances, big variations are also seen (Das AJ 2011, Hashim P 2011, Joshi K et al 2013).

Macronutrient and mineral contents of *Centella asiatica* are summarized in Table 1 and Table 2. Generally, the herb is low in protein (2.4%), carbohydrate (6.7%), and fat (0.2%). *Centella asiatica* has been reported to contain about 87.7% moisture, 5.4% insoluble dietary fiber, and 0.49% soluble dietary fiber, and 17.0 mg/100 g phosphorus, 14.9 mg/100 g iron, and 107.8 mg of sodium.

Table 1: Macronutrient Percentage of *Centella asiatica* (mg/100g)

Protein	Carbohydrate	Fiber	Moisture	Fat	Study
-	6.70	1.60	87.70	0.20	Hashim (2011)
2.40	-	5.92	84.60	-	Joshi and Chaturvedi (2013)
9.94	51.92	18.33	84.37	-	Das (2011)

Table 2: Mineral Content of the *Centella asiatica* (mg/100 g)

Na	K	Ca	mg	P	Fe	Study
21.00	-	-	-	32.00	5.60	Hashim (2011)
107.80	34.00	174.00	87.00	17.00	14.86	Joshi and Chaturvedi (2013)
-	-	1.06.00	-	370.00	32.00	Das (2011)

Values of the nutrient composition suggest that *Centella asiatica* is a good source of dietary fibers which is a significantly important nutrient component. Dietary fiber intake provides many health benefits. A generous intake of dietary fiber reduces risk of developing coronary heart disease, stroke, hypertension, diabetes, obesity, and certain gastrointestinal disorders, and provides many other health benefits (Anderson JW et al 2009). Total calories in 100 g of *Centella asiatica* are 37.0 kcal (Hashim P 2011). In general, *Centella asiatica* ca contains a high concentration of potassium (345 mg) and calcium (171 mg). Potassium intake reduces the risk of stroke, kidney stones, renal damages, and many heart-related problems. Calcium is also an important structural component of bone. Adequate calcium intake throughout childhood and adolescence is needed to achieve maximum bone mass in young adulthood which is an important determinant of bone mineral status in later life. *Centella asiatica* can be used as a nonexpensive nutritional source of both potassium and calcium. However, mineral content of the different morphotypes of *Centella asiatica* can drastically vary. *Centella asiatica* is also rich in vitamin C (48.5 mg/100 g), B1 (0.09 mg/100 g), B2 (0.19 mg/100 g), niacin (0.1 mg/100 g), carotene (2649 µg/100 g), and vitamin A (442 µg/100 g) (Hashim P 2011, Joshi K et al 2013).

IV. PHYTOCHEMISTRY AND BIOACTIVE COMPOUNDS OF *CENTELLA ASIATICA*

Centella asiatica has long been used as folklore medicine for the treatment of a variety of diseases. Chemically it has been identified leading to therapeutic properties. Asiatic acid, asiaticoside, and madecassoside form the major constituents responsible for pharmacological value apart from being rich in flavonoids and terpenoids (Roy et al 2013). Centelloid was term given for different constituents of secondary metabolites produced by plant which mainly comprised of pentacyclic triterpenoid saponins (James and Dubery 2009). P-cymene-(44%) along with other volatile compounds was found to be in a prominent amount in the essential oil of *Centella asiatica* on analysis with gas chromatography-mass spectrometry (GC-MS) (Francis and Thomas 2016). Centellin, asiatic, and centellicin were isolated from the aerial part of the plant, and further, their structures had been determined using 2D nuclear magnetic resonance technique (Siddiqui et al 2007). From plant extracts using high-performance liquid chromatography to identify bioactive compounds, madecassoside, asiaticoside, madecassic acid, and Asiatic acid were found in the significant amount (Inamdar et al 1996). A quantitative estimation of triterpenoids showed highest asiaticoside content (6.42%) in leaf samples collected in Mangoro region (Randriamampionona et al 2007). New triterpene and a saponin, 2α,3β,23-trihydroxyurs-20-en-28-oic acid and 2α,3β,23-trihydroxyurs-20-en-28-oic acid O-α-l-rhamnopyranosy-(1→4)-O-β-dglucopyranosyl (1→6)-O-β-d glucopyranosyl ester, have been isolated from the aerial part of *Centella asiatica*, and their structures were determined using spectral methods (Yu et al 2007).

Centella asiatica is considered as an enriched source of different active compounds as shown in Table 3. The main active compounds of *Centilla asiatica* are pentacyclic triterpenes (asiatic acid, madecassic acid, asiaticoside and madecassoside) (Puttarak and Panichayupakaranant 2012).

Table 3: Main active compounds of *Centella asiatica*

Main Groups	Active Compounds	References
Terpenoids	Triterpenes, asiaticoside, centelloside, madecassoside, brahmoside, brahminoside (saponin glycosides), asiaticentoic acid, centellic acid, centoic acid, madecassic acid, terminolic acid and betulic acid.	(Barnes et al 2007), (Jamil et al 2007)
	Various terpenoids: β-caryophyllene, trans β-farnesene and germacrene D (sesquiterpenes), α-pinene and β-pinene	(Barnes et al 2007), (Jamil et al 2007)
Phenols	Flavonoids: kaempferol, kaempferol-3-o-β-d-glucuronide, castilliferol, quercetin, quercetin-3-o-β-d-glucuronide, castillicetin, apigenin, rutin, luteolin, naringin	(Bhandari et al 2007, Zheng and Qin 2007, Chong and Aziz 2013)
	Phenylpropanoids: rosmarinic acid, chlorogenic acid, 3,4-di-o-caffeoyl quinic acid, 1,5-di-o-caffeoyl quinic acid, 3,5-di-o-caffeoyl quinic acid, 4,5-di-o-caffeoyl quinic acid, isochlorogenic acid	(Chong and Aziz 2013)
	Tannin: tannin, phlobatannin	(Chong and Aziz 2013)

V. PHARMACOLOGICAL ACTIVITIES OF *CENTELLA ASIATICA*

Centella asiatica has been significantly drawn the attention of scientific groups in the recent years as it has multiple usages in the treatment of ailments. In Figure 2, major pharmacological usage in the treatment of ailments has been outlined followed by its detailed description.

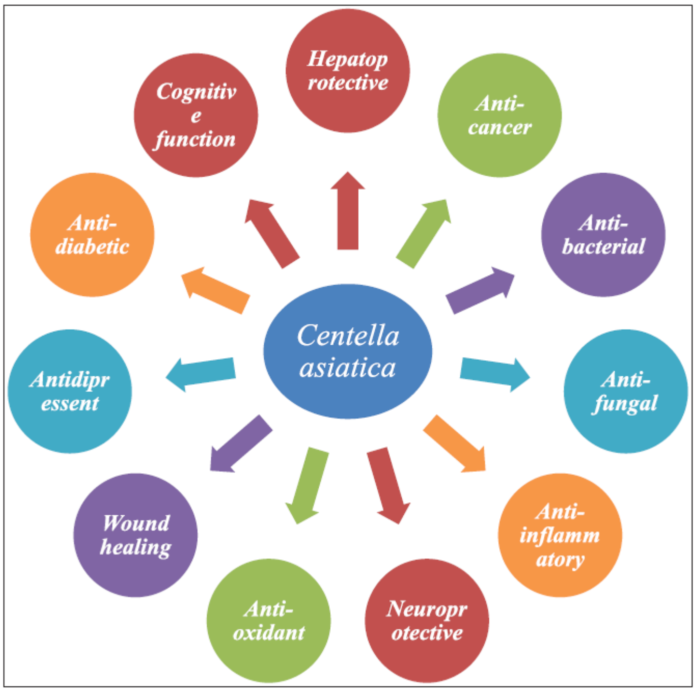

Figure 2: Pharmacological activities of *Centella asiatica*

Anticancer Activities

On A549 and PC9/G lung cancer, cell line inhibitory concentration 50 (IC_{50}) values of A-3 were 26.03 ± 2.47 and 25.57 ± 0.51, respectively, due to the presence of asiatic acid as major component (Wang et al 2013). Against the cell lines of human breast cancer (MDA MB-231), mouse melanoma (B16F1), and rat glioma (C6), the aqueous extract of *Centella asiatica* had shown inhibitory activity with IC_{50} values of 698, 648, and 1000 μg/mL respectively (Pittella et al 2009). The methanolic extract of *Centella asiatica* (Linn) showed inhibitory effect on MCF-7 cell lines, and induced apoptosis in MCF-7 cells as indicated by nuclear condensation, increased annexin staining, loss of mitochondrial membrane potential, and induction of DNA breaks was identified by TUNEL reactivity (Babykutty et al 2009). The effect of *Centella asiatica* juice was checked on human HepG2 cell line using MTT assay, and it showed cytotoxic effects on tumor cells in a dose-dependent manner. At a concentration above 0.1% of juice, a higher amount of DNA damage and apoptotic cell death was observed on human HepG2 cell line (Hussin et al 2014).

Asiatic acid was evaluated for antiproliferative effect in lung cancer cells using MTT assay. Oral administration of asiatic acid inhibited weight and tumor volume significantly in lung cancer xenograft model (Wu et al 2017). In another study, asiatic acid showed induced apoptosis and decreased viability in human melanoma SK-MEL-2 cells in a dose-dependent manner (Park et al 2005). Asiatic acid derived from *Centella asiatica* showed antiproliferative effects on RPMI 8226 cells. It decreased the expression levels of focal adhesion kinase (FAK), and the probable mechanism of asiatic acid may be related to the inhibition of signal transduction mediated by FAK (Zhang et al 2013). Asiatic acid, asiaticoside, and madecassic acid was the major composition of titrated extract of *Centella asiatica*, and asiaticoside reduces melanogenesis in B16F10 mouse melanoma by checking tyrosinase mRNA expression (Kwon et al 2013). In long-term culture at a concentration of 8 ug/ml, partially purified fractions inhibited the growth of mouse lung fibroblast (L-929) cells (Babu et al 1995). Reduction of up to 50% in viability was observed in ovarian cancer cells treated with 40 ug/ml concentration of asiatic acid, and it also showed cell cycle arrest at the G0/G1 phase and increased apoptosis by 7-10 folds (Ren et al 2016). Induction of apoptosis was observed in A-549 cell line due to presence of asiatic acid which helped in regulation of miR-1290, BCL2 protein level, and cell cycle regulation (Kim et al 2014).

Anti-inflammatory Activities

Anti-inflammation is widely used methodology in experimental oncology which helps to examine the inflammation defensive potential of natural products (betulinic acid, α-amyrin acetate, lupeol acetate, oleanolic acid, and ursolic acid) and synthetic entities (Sultana et al 2012). Terpenoid is major constituents among secondary metabolites secreted by plants. It helps to cope up stress condition and supports defense activities. Plants with medicinal properties are rich in these compounds such as ceramide and different forms of terpenoids (Prakash 2017). Pentacyclic triterpenoid and saponins are collectively known as centelloids. Among different constituents, triterpenoid saponins were mainly expected to be responsible for therapeutic actions (James and Dubery 2009). Hypotonicity-induced human red blood cell membrane breakdown was inhibited by *Centella asiatica*. At different concentrations, membrane stabilization was observed for diclofenac sodium and methanolic extracts, and at a dose of 2000 μg/ml, maximum membrane stabilization of *Centella asiatica* extracts was noticed to be 94.97% (Chippada et al 2011). At concentration of 2 mg/kg, the *Centella asiatica* extract showed moderate anti-inflammatory property on prostaglandin E2-induced inflammation in a dose-dependent manner (Somchit et al 2004). In another study, the aqueous and alcoholic extract of *Centella asiatica* showed 46.31% and 71.18%, respectively, inhibition of edema after 3 hrs, while the standard ibuprofen showed an inhibition of 66.66% (George et al 2009). At the 4^{th} and 5^{th} hrs, after λ-carrageenan (Carr) supplementation, the asiatic acid reduced paw edema by regulation of catalase, superoxide dismutase (SOD), and glutathione in the liver tissue (Huang et al 2011). In another study, measurement of paw size was taken before carrageenan injection and then 1, 2, 3, and 4 hrs after carrageenan injection. It was observed that the methanolic extract showed significant inhibition, and the highest inhibition was at 3 hrs at 200 mg/kg dose which was slightly lower than indomethacin effect (Saha et al 2013).

Antidepressant Activities

Compared to diazepam *Centella asiatica* possesses antianxiety effect but has no effect on behavioral despair (Bhavna and Jyoti 2011). Total triterpenes and imipramine from *Centella asiatica* were evaluated for antidepressant activity using forced swimming test, the result showed a reduction in stillness duration and regulated amino acid levels (Chen et al 2003). In another study, decrease in corticosterone level in serum and enhanced 5-HT, NE, DA and their metabolites 5-HIAA and MHPG in rat brain were observed (Chen et al 2005). Standardized extract showed a reversal of physiological and behavioral changes following OBX-induced depression in rats (Kalshetty 2012). Forced swim test was performed in male Sprague-Dawley rat treated with asiatic acid and midazolam+asiatic acid, significant result was observed in the ration of open-arm time, maximum speed, and time spent in the asiatic acid group and the midazolam+ asiatic acid group ($p<0.05$) (Ceremuga et al 2015).

Antidiabetic Activities

Antidiabetic properties of leaves extract of *Centella asiatica* was evaluated in alloxan-induced rat by administering extract at a concentration of 250, 500, and 1000 mg/kg after 3 hrs of ingestion reduction in blood glucose level was noticed by 32.6%, 38.8%, and 29.9%, respectively (Rahman et al 2012). Effect of ethanol extract was tested in streptozotocin (50 mg/kg)-induced Wistar rats. Studying the serum glucose, urea cholesterol, lipid, liver glycogen level, and body weight, the antidiabetic activity of extract at concentration of 200 mg/kg was noticed (Gayathri et al 2011). In a study, lower inhibitory activities of α-amylase of *Centella asiatica* extract and rutin were observed when compared to acarbose and an anti-diabetic drug (Supkamonseni et al 2014). Extract of *Centella asiatica* led to reducing blood glucose level in dose-dependent manner by 29.4%, 32.8%, 33.6%, and 35.7%, respectively, at doses of 50, 100, 200, and 400 mg per kg body weight (Haque et al 2013). In alloxan-induced rats, reduction in blood glucose level was observed at a dose level of 50 mg/kg b.wt. of *Centella asiatica* juice (Rahman et al 2012). The effect of intestinal disaccharides and alpha amylase was inhibited, and lowered glucose absorption was observed when supplemented with plant extract (Kabir et al 2014). Long-term administration of plant extract reversed the blood glucose level to normal in obese diabetic rat (Maulidiani et al 2016). Asiatic acid was found to reduce blood glucose level in Goto-Kakizaki (GK) rat by enhancing fibrosis of islets in diabetes which plays a vital role in the prevention of islets dysfunction (Wang et al 2015). In diabetic Wistar rat model, asiatic acid showed to preserve and restore beta cell mass (Liu et al 2010).

Antioxidant Activities

Free radical and reactive oxygen species (ROS) are the main reason behind aging. All organisms have a mechanism to deal with such reactive groups, free radical scavengers provide protection to the organism. The plant extract obtained from Turkey and India was compared with a standardized extract of plant obtained from China. The three extract at concentration of 250, 500, 1000, and 2000 µg/mL showed radical scavenging activity for 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay: CA-STD>CA-TR>CA-IND (Orhan et al 2013). *Centella asiatica* extract and powder was evaluated for reduction in oxidative stress in Sprague-Dawley rats. Results showed a decrease in the generation of ROS and oxidative stress in the rats. It was also noted that there was a significant decrease in SOD level (Hussin et al 2007). Essential oil of *Centella asiatica* extracted through steam distillation showed to be excellent antioxidant for food containing lipids. Its activity was quite comparable with the synthetic antioxidant butylhydroxyanisole (BHA) (Raza et al 2009). Polyphenol, flavonoid, β-carotene, tannin, Vitamin C, and DPPH compounds are readily found in *Centella asiatica* contributing to significantly higher antioxidant activity in the herb (Chandrika et al 2015). Crude methanolic extract on continuous supplementation for 14 days resulted in increase in level of antioxidant enzymes and ascorbic acid level reduced in lymphoma-bearing mice (Jayashree et al 2003). Extracts of *Centella asiatica* in different solvents such as chloroform, hexane, acetone, ethyl acetate, methanol, and water were assessed for antioxidant potential. The DPPH and hydroxyl radical scavenging activity were tested for methanolic extract which showed the IC_{50} value of 0.07 mg/ml and 500 µg/ml, respectively (Anand et al 2010).

Woundhealing Activities

An increase in DNA, protein, and collagen content of granulation tissues was observed on supplementation of extract of *Centella asiatica* resulting in collagen synthesis and cellular proliferation at wound site (Suguna et al 1996). The extract of *Centella asiatica* considerably enhanced the wound breach power in incision model when compared to controls ($p<0.001$), wound contraction rate was noticeably enhanced as compared to control wounds ($p<0.001$), and wounds epithelized faster when treated with an extract of *Centella asiatica* (Shetty et al 2006). Rats treated with extract showed a better tensile strength of wound after 7 days of wound infliction when compared with control (Somboonwong et al 2012). A study on ethanol-induced gastric lesion oral administration of *Centella asiatica* (0.05, 0.25, and 0.50 g/kg) before ethanol administration considerably lowered mucosal myeloperoxidase activity checked gastric lesions formation (58% to 82% reduction) and in a dose-dependent manner (Cheng et al 2000). Fibroblast division and collagen synthesis were enhanced in wound on treatment with extract of *Centella asiatica* (Yao et al 2017).

Antimicrobial Activities

Methanol hot extract from *Centella asiatica* leaves was taken to check the antibacterial activity which was assessed by zone of inhibition and minimum inhibitory concentration (MIC) value (2 µg/disc) by disc diffusion method. *In-vitro* antibacterial activity of the plant extract against *Staphylococcus aureus* ATCC 25923 and methicillin resistance *S. aureus* (wild type) showed a zone of inhibition of 5 mm and 7 mm respectively (Zaidan et al 2005). In a study, it was observed that essential oil extract showed antibacterial properties against Gram-positive (*Bacillus subtilis* and *S. aureus*) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Shigella sonnei*) with MIC values ranging from 1.25 to 0.039 mg/ml (Oyedeji et al 2005). *Bacillus cereus* and *Listeria monocytogenes* 10403S were selected to study the antibacterial activity in *Centella asiatica* under both normal and osmatic stress condition. At 95% ethanolic extract, antibacterial activity was enhanced twice under osmotic stress condition. The MIC of *Centella asiatica* was observed to be 16 µl/ml against *B. cereus* while 8 µl/ml for L. monocytogenes10403S (Pitinidhipat et al 2015). MS media was used to culture leaf explants, and its antibacterial activity against *B. cereus*, *E. coli*, *S. aureus*, and *P. aeruginosa* was evaluated; methanol extracts of leaf and callus displayed maximum inhibitory effect against the tested organisms (Sekar et al 2011).

The petroleum ether, ethanol, chloroform, n-hexane, and aqueous extract of *Centella asiatica* showed activity against *Aspergillus niger* and C. *albicans* with a zone of inhibition of 14, 16, 13, 13, and11 mm and 13, 15, 15, 11, and 9 mm, respectively. The control Ketoconazole (10 µg) showed the inhibition of 12 mm (Dash et al 2011). Ethanolic extract of *Centella asiatica* was checked for antifungal activity against *Aspergillus flavus*, and *Penicillium citrinum* exhibited the strongest antimold activity (percentage mycelial inhibition = 26.3 mm) (Dhiman et al 2016). 100% ethanolic extract of *Centella asiatica* showed a zone of inhibition of 15.4 mm against *A. niger* (Idris and Nadzir 2017). Following agar well diffusion method, antimicrobial activity was checked for ethanolic extract of plant against *A. niger* and *Candida albicans*, an inhibition of 16 and 15 mm was observed, respectively, while control ketoconazole (10 µg) gave a inhibition zone of 12 and 10 mm (Dash et al 2011). Against *Candida albicans*, on an average 5 mm, zone of inhibition was observed while the standard miconazole nitrate showed an inhibition of 20 mm (Sultan et al 2014).

Cognitive Functions

Asiatic acid was found to prevent spatial working memory and reduction of neurogenesis defects in the hippocampal region caused by 5-FU chemotherapy (Chaisawang et al 2017). Water extract of *Centella asiatica* was observed to enhance synaptic differentiation and dendritic arborization with reference to Aβ which causes cognitive improvement (Gray et al 2017). In a study, *Centella asiatica* extract was supplemented for weeks in defined concentration results showed to be effective in the treatment of cognitive function impairment after stroke (Farhana et al 2016). Asiatic acid has potential to restore the impairment of cell proliferation, spatial working memory caused by treatment with valproic acid (Umka et al 2016). Water extract helped to improve cognitive function by activation of antioxidant response gene and mitochondrial biogenesis (Gray et al 2016), normalized calcium homeostasis (Gray et al 2015). In another study, asiatic acid was found to enhance hippocampal neurogenesis which can serve as potent cognitive enhancer (Sirichoat et al 2015). Asiaticoside isolated from hydrocotyle sibthorpioides helps in scavenging free radical enhancing activity of antioxidant enzymes, improving synaptic plasticity, reducing the level of Aβ, and reversing abrupt changes in AchE activity (Lin et al 2013). In cognitive-related disorders, mitochondrial dysfunction and oxidative stress have major role, in a study carried out aluminum-induced cognitive dysfunction and mito-oxidative damage C. asiatica have proved to carry neuroprotective potential (Prakash and Kumar 2013). The study was done in primary culture of rat cortical neurons to check the activity of subtypes of PLA2, asiaticoside present in extract inhibited cPLA2 and sPLA2 activities (Defillipo et al 2012). On experiment conducted on mice model oral supplementation of asiatic acid (100 mg/kg), significant improvement in cognitive function was observed in the Morris maze test and retained glutathione and lipid peroxidation and SOD activity in cortex and hippocampus to control levels (Kumar and

Prakash 2011). In another study, *Centella asiatica* proved to have a protective role against D-glucose-induced biochemical, behavioral, and mitochondrial dysfunction in mice (Kumar et al 2009). Acute administration of asiatic acid was studied on male Sprague-Dawley rats for memory and learning, treatment at 30 mg/kg of asiatic acid significantly improved memory (Nasir et al 2011). The healing effect of *Centella asiatica* was observed against colchicine-induced cognitive impairment (Kumar et al 2009) and lead acetate-induced changes in oxidative biomarkers in the central nervous system (Ponnusamy et al 2008). Cyclic AMP response element binding protein phosphorylation level was enhanced in primary culture of rat embryonic cortical cells on treatment with plant extract, thus improving memory function (Xu et al 2008). In another finding, it was found that high dose of plant extract-enhanced memory and increased N100 constituent amplitude of event-related potential (Wattanathorn et al 2008). In an intracerebroventricular streptozotocin model of Alzheimer's disease in rat plant, aqueous extract was found effective in combating the cognitive deficit and oxidative stress (Veerendra Kumar and Gupta 2003).

Hepatoprotective Activities

Effect of methanolic extract of *Centella asiatica* was evaluated in Type 2 diabetes mellitus, hepatic concentrations of interleukin-1β, MCP-1, and tumor necrosis factor alpha in diabetic control rats orally treated with deionized water, group were reduced to 68%, 75%, and 63% of normal control rats orally treated with deionized water values, respectively (Oyenihi et al 2017). In dimethylnitrosamine-induced liver injury *Centella asiatica* noticeably enhanced fibrosis of liver tissues by mass periportal, bridging necrosis, intralobular degeneration, and focal necrosis (Choi et al 2016). On INH-treated albino rats, *Centella asiatica* (100 mg/kg bw) dose was found effective to improve liver histology (Ghosh et al 2017). In cyclophosphamide (CYP)-induced hepatotoxicity in rats, *Centella asiatica* triterpene saponins regulated hepatic function by restoring cytokine production (Duggina et al 2015). Hepatoprotective activity of plant extract was checked against CCl_4-induced liver injury, and the extract showed hepatoprotective activity most probably due to the presence of asiaticoside (14.5%) in the extract (Antony et al 2006). The functional group of asiatic acid was modified at C2, C3, C23, and C28. Compound 9 showed hepatoprotective effects against GaIN-induced hepatotoxicity (66.4% protection at 50 μM) and moderate hepatoprotective activities against CCl4-induced hepatotoxicity (20.7% protection at 50 μM) (Jeong et al 2007). Asiatic acid protects liver injury by onset of Smad7-dependent inhibition of TGF-beta/Smad-assisted fibrogenesis (Tang et al 2012). Conventionally, used plants to get rid of liver dysfunction might, therefore, could be potential source for new hepatoprotective compounds for development as pharmaceutical entities (Rajalingam et al 2016).

Neurodegenerative Disorders (NDD)

Description of Neurodegenerative Disorders: Neurodegenerative diseases represent a major threat to human health. These age-dependent disorders are becoming increasingly prevalent, in part because the elderly population has increased in recent years (Heemels, 2016). Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias. These diseases are diverse in their pathophysiology – with some causing memory and cognitive impairments and others affecting a person's ability to move, speak and breathe (Abeliovich and Gitler, 2016; Canter et al., 2016; Taylor et al., 2016; Wyss-Coray, 2016).

Risk factors of Neurodegenerative Disorders: Virtually every review article on NDDs cites age as a significant risk factor for developing these disorders. For example, Alzheimer's disease is rare in individuals younger than 50 but prevalence begins rising an additional 0.5% per year after age 65, increasing to about 8% per year after age 85. Similarly, rare before the sixth decade of life, Parkinson's disease prevalence may be as high as 2% for individuals over age 65, increasing every year thereafter. Recent evidence suggests that the accumulation of senescent nervous system cells, a natural consequence of aging, may predispose individuals toward developing NDDs or accelerate progression of these diseases once they take hold. Investigating the link between senescence and NDDs has been hindered by the lack of universal markers for senescent neuronal cells. Age is not the only risk factor for Parkinson's, as the lifetime risk for developing the disease is 4.4% for men and 3.7% for women. A recent paper suggested that "sex might constitute an important factor for AD (Alzheimer's disease) patient stratification and personalized treatment." Sex differences related to immune responses to neurodegeneration, affecting both susceptibility and disease progression, are also apparent in multiple sclerosis, which women develop more frequently than men, but which progresses more slowly and less frequently in females. Similarly, a 2018 article reviewing nearly 300 papers on sex differences and cognitive decline in Alzheimer's disease confirmed that women "are at significantly higher risk of developing" Alzheimer's, and that their cognitive outcomes were poorer than men's. Moreover, the degree to which underlying health issues such as obesity, cardiovascular disease, and lifestyle factors affect the course of various dementias also varies by sex. While females are at greater risk for developing Alzheimer's, men are more susceptible to vascular dementia. The underlying mechanisms of these differences are still unknown. Part of the answer might lie in the physiological differences in gray matter composition that persist between the sexes from birth throughout life. Females have a higher gray matter density than men but significantly lower gray matter volume and mass, and these differences prevail in all relevant regions of the brain (Angelo DePalma 2021).

Neuroprotective Activities of Centella asiatica: Neuroprotection aspect of *Centella asiatica* mainly involves enzyme inhibition, prevention of amyloid plaque formation in Alzheimer's disease, dopamine neurotoxicity in Parkinson's disease, and reducing oxidative stress (Orhan 2012). Water extract of *Centella asiatica* was evaluated on the activity of subtypes of phospholipase A2 (PLA2) in primary cultures of rat cortical neurons, asiaticoside present in extract inhibited cPLA2 and sPLA2 activities (Defillipo et al 2012). In male Sprague-Dawley rats, improved learning and memory were observed on acute administration of asiatic acid (Nasir et al 2011). Neuroprotective potential of modern medicine constituents of the plant includes asiatic acid, madecassic acid, and brahmaside as well as flavonoids madecassoside and madesiatic acid (Thomas and Thomas 2015). *Centella asiatica* was explored for neuroprotective effect on cell death and cognitive irregulation in aluminum-treated rat. Significant improvement in memory performance, oxidative defense was observed on chronic administration of *Centella asiatica* (Prakash and Kumar 2013). The plant is known to utilize neuroprotective effects by attenuating the changes in an animal model such as pathological neurobehavioral and neurochemical properties. Phosphoinositides-assisted cytodynamics and synaptic function show the neuroprotective effects of asiaticoside in the rat which includes mode of ROT-infused hemiparkinsonism (Gopi et al 2017).

Centella asiatica and compounds such as flavonoids, celastrol, trehalose, lycopene, sesamol, resveratrol, and curcumin has gained a lot of interest for their therapeutic potential. Table 4 summarizes some of the commonly used natural compounds for their neuroprotective effect.

Table 4: Natural compounds with neuroprotective effect

S. No.	Medicinal Plants/Compounds	Constituents	Applications	References
1	*Centella asiatica* extract	Asiaticoside, madecassoside, asiatic and madecassic acids	Inhibit the 3-NP induced depletion Protects against mitochondrial dysfunction induced by 3-NP	(Choudhary et el 2013, Shinomol and Muralidhara 2008)
2	Flavonoids	Naringin; Hesperidin; Kaempferol;	Inhibit nitric oxide synthase Scaveng ROS & reactive nitrogen species	(Choudhary et el 2013, Lopez-Lopez et al 2004)
3	*Tripterygium wilfordi*	Triptolide	Inhibit pro-inflammatory cytokines production, NO synthase peroxidation of lipid Ability to attenuate loss of dopaminergic neurons & dopamine depletion	(Choudhary et el 2013, Allison et al 2001)
4	*Sesamum indicum* Linn	Sesamol	Protect against neuroinflammation in hippocampus neurons	(Hsu et al 2008, Choudhary et el 2013)
5	*Convolvulus pluricaulis* extract	-	Inhibits the enzymatic activity of acetylcholine esterase. Helps in maintaining the level of various mRNA receptors such as M1 receptors, nerve growth-factor tyrosine kinase A receptor, choline acetyl transferase	(Bihaqi et al 2011)

VI. SUMMARY

The findings of this review of literature delineated that the *Centella asiatica* finds widespread use in several traditional systems of medicine with an array of health-care applications. It is widely accepted that plant has got neuroprotective activities and helpful in brain improvement. Plants have proved to bear low toxicity and higher efficacy in clinical treatment with prominent activities such as anticancer, antibacterial, antifungal, anti-inflammation, neuroprotection, antioxidant, wound healing, and antidepressant as mentioned above.

VII. FUTURE PERSPECTIVES

With wide range of pharmacological potentials of *Centella asiatica* has been frequently used as medicine in Indian Herbal Pharmacopoeia, the German Homeopathic Pharmacopoeia, European Pharmacopoeia and the Pharmacopoeia of the People's Republic of China. Owing to the high therapeutic potential, it is of high demand in pharmaceutical industries which escorts to its overexploitation resulting in the relapsing of the population of *Centella asiatica* to a precarious level that a ban on its collection from their natural habitat has been recommended. *Centella asiatica*, thus recognized as threatened medicinal herb is endemic to Western Ghats of South India. Thus, it has become imperative to develop alternative approaches for its conservation, in order to protect it from the verge of extinction. *In-vitro* culture technique offers a viable tool for the mass propagation of plant and conservation of rare, threatened and endangered germplasm.

REFERENCES

1. Abeliovich A, Gitler AD. Defects in trafficking bridge Parkinson's disease pathology and genetics. Nature. 2016;539(7628):207-16.
2. Allison AC, Cacabelos R, Lombardi VR, Álvarez XA, Vigo C. Celastrol, a potent antioxidant and anti-inflammatory drug, as a possible treatment for Alzheimer's disease. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2001;25(7):1341-57.
3. Anand T, Mahadeva N, Phani KG, Farhath K. Antioxidant and DNA damage preventive properties of *Centella asiatica* (L) Urb. Pharm J 2010;2(17):53-8.
4. Anderson JW, Baird P, Davis RH, Ferreri S, Knudtson M, Koraym A, Waters V, Williams CL. Health benefits of dietary fiber. Nutrition reviews. 2009;67(4):188-205.
5. Angelo DePalma. Neurodegenerative Disease Research Update; Web address: https://www.biocompare.com/Editorial-Articles/563155-Neurodegenerative-Disease-Research-Update. (Last accessed on December 10, 2021).
6. Antony B, Santhakumari G, Merina B, Sheeba V, Mukkadan J. Hepatoprotective effect of *Centella asiatica* (L) in carbon tetrachloride-induced liver injury in rats. Indian J Pharm Sci 2006;68(6):772.
7. Arora, D., M. Kumar, and S. D. Dubey. "*Centella asiatica*-a Review of Its Medicinal Uses and Pharmacological Effects." Journal of Natural remedies 2.2 (2002): 143-149.

8. Babu TD, Kuttan G, Padikkala J. Cytotoxic and anti-tumour properties of certain taxa of Umbelliferae with special reference to *Centella asiatica* (L.) Urban. J Ethnopharmacol 1995;48(1):53-7.
9. Babykutty S, Padikkala J, Sathiadevan P, Vijayakurup V, Azis T, Srinivas P, et al. Apoptosis induction of Centella asiatica on human breast cancer cells. Afr J Tradit Complement Altern Med 2009;6(1):9-16.
10. Bhavna D, Jyoti K. *Centella asiatica*: The elixir of life. Int J Res Ayurveda Pharm 2011;2(2):431-8.
11. Bihaqi SW, Singh AP, Tiwari M (2011) In vivo investigation of the neuroprotective property of *Convolvulus pluricaulisin* scopolamine-induced cognitive impairments in Wistar rats. Indian J Pharmacol. 43(5):520–525
12. C. Zheng and L. Qin, “Chemical components of *Centella asiatica* and their bioactivities,” Journal of Chinese Integrative Medicine, vol. 5, pp. 348–351, 2007.
13. Canter R. G., Penney J. and Tsai L.-H. (2016). The road to restoring neural circuits for the treatment of Alzheimer's disease. Nature 539, 187-196.
14. Ceremuga TE, Valdivieso D, Kenner C, Lucia A, Lathrop K, Stailey O, Taylor A. Evaluation of the anxiolytic and antidepressant effects of asiatic acid, a compound from Gotu kola or Centella asiatica, in the male Sprague Dawley rat. AANA J 2015;83(2):91-8.
15. Chaisawang P, Sirichoat A, Chaijaroonkhanarak W, Pannangrong W, Sripanidkulchai B, Wigmore P, et al. Asiatic acid protects against cognitive deficits and reductions in cell proliferation and survival in the rat hippocampus caused by 5-fluorouracil chemotherapy. PLoS One 2017;12(7):e0180650.
16. Chandrika UG, Kumara PA. Gotu Kola (*Centella asiatica*): Nutritional properties and plausible health benefits. Adv Food Nutr Res 2015; 76:125-57.
17. Chen Y, Han T, Qin L, Rui Y, Zheng H. Effect of total triterpenes from *Centella asiatica* on the depression behavior and concentration of amino acid in forced swimming mice. Zhong Yao Cai 2003;26(12):870-3.
18. Chen Y, Han T, Rui Y, Yin M, Qin L, Zheng H. Effects of total triterpenes of *Centella asiatica* on the corticosterone levels in serum and contents of monoamine in depression rat brain. Zhon Yao Cai 2005;28(6):492-6.
19. Cheng CL, Koo MW. Effects of *Centella asiatica* on ethanol induced gastric mucosal lesions in rats. Life Sci 2000;67(21):2647-53.
20. Chippada SC, Volluri SS, Bammidi SR, Vangalapati M. In vitro anti-inflammatory activity of methanolic extract of Centella asiatica by HRBC membrane stabilisation. Rasayan J Chem 2011;4(2):457-60.
21. Choi MJ, Zheng HM, Kim JM, Lee KW, Park YH, Lee DH. Protective effects of *Centella asiatica* leaf extract on dimethylnitrosamine-induced liver injury in rats. Mol Med Rep 2016;14(5):4521-8.
22. Choudhary S, Kumar P, Malik J (2013) Plants and phytochemicals for Huntington’s disease. Pharm Rev. 7(14):81–91.
23. Das AJ. Review on nutritional, medicinal and pharmacological properties of *Centella asiatica* (Indian pennywort). Journal of Biologically Active Products from Nature. 2011;1(4):216-28.
24. Dash BK, Faruquee HM, Biswas SK, Alam MK, Sisir SM, Prodhan UK. Antibacterial and antifungal activities of several extracts of *Centella asiatica* L. against some human pathogenic microbes. Life Sci Med Res 2011; 2011:1-5.
25. Defillipo PP, Raposo AH, Fedoce AG, Ferreira AS, Polonini HC, Gattaz WF, et al. Inhibition of cPLA2 and sPLA2 activities in primary cultures of rat cortical neurons by *Centella asiatica* water extract. Nat Prod Commun 2012;7(7):841-3.
26. Dhiman R, Aggarwal N, Aneja KR, Kaur M. In vitro antimicrobial activity of spices and medicinal herbs against selected microbes associated with juices. Int J Microbiol 2016; 2016:9015802.
27. Duggina P, Kalla CM, Varikasuvu SR, Bukke S, Tartte V. Protective effect of centella triterpene saponins against cyclophosphamide-induced immune and hepatic system dysfunction in rats: Its possible mechanisms of action. J Physiol Biochem 2015;71(3):435-4.
28. Farhana KM, Malueka RG, Wibowo S, Gofir A. Effectiveness of Gotu Kola extract 750/mg and 1000/mg compared with folic acid 3/mg in improving vascular cognitive impairment after stroke. Evid Based Complement Alternat Med 2016; 2016:2795915.
29. Francis SC, Thomas MT. Essential oil profiling of *Centella asiatica* (L.) Urb-a medicinally important herb. South Indian J Biol Sci 2016;2(1):169-73.
30. Gayathri V, Lekshmi P, Padmanabhan RN. Anti-diabetes activity of ethanol extract of *Centella asiatica* (L.) urban (whole plant) in Streptozotocin-induced diabetic rats, isolation of an active fraction and toxicity evaluation of the extract. Int J Med Aromat Plants 2011;1(3):278-6.
31. George M, Joseph L, Ramaswamy. Anti-allergic, anti-pruritic, and anti-inflammatory activities of *Centella asiatica* extracts. Afr J Tradit Complement Altern Med 2009;6(4):554-9.
32. Ghosh K, Indra N, Jagadeesan G. The ameliorating effect of *Centella asiatica* ethanolic extract on albino rats treated with isoniazid. J Basic Clin Physiol Pharmacol 2017;28(1):67-7.
33. Gopi M, Arambakkam Janardhanam V. Asiaticoside: Attenuation of rotenone induced oxidative burden in a rat model of hemiparkinsonism by maintaining the phosphoinositide-mediated synaptic integrity. Pharmacol Biochem Behav 2017; 155:1-15.
34. Gray NE, Harris CJ, Quinn JF, Soumyanath A. Centella asiatica modulates antioxidant and mitochondrial pathways and improves cognitive function in mice. J Ethnopharmacol 2016; 180:78-6.
35. Gray NE, Sampath H, Zweig JA, Quinn JF, Soumyanath A. *Centella asiatica* attenuates amyloid-ß-induced oxidative stress and mitochondrial dysfunction. J Alzheimers Dis 2015;45(3):933-46.
36. Gray NE, Zweig JA, Murchison C, Caruso M, Matthews DG, Kawamoto C, et al. *Centella asiatica* attenuates Aß-induced neurodegenerative spine loss and dendritic simplification. Neurosci Lett 2017; 646:24-9.
37. Haque S, Naznine T, Ali M, Azad TT, Morshed T, Afsana NA, et al. Antihyperglycemic activities of leaves of *Brassica oleracea*, *Centella asiatica* and *Zizyphus mauritiana*: Evaluation through oral glucose tolerance tests. Adv Nat Appl Sci 2013;7(5):519-26.
38. Hashim P. Centella asiatica in food and beverage applications and its potential antioxidant and neuroprotective effect. International Food Research Journal. 2011;18(4):1215.

39. Hsu DZ, Wan CH, Hsu HF, Lin YM, Liu MY (2008) The prophylactic protective effect of sesamol against ferric–nitrilotriacetate-induced acute renal injury in mice. Food Chem Toxicol 46(8):2736–2741.
40. Huang SS, Chiu CS, Chen HJ, Hou WC, Sheu MJ, Lin Y, et al. Antinociceptive activities and the mechanisms of anti-inflammation of asiatic acid in mice. Evid Based Complement Alternat Med 2011:895857.
41. Hussin F, Eshkoor SA, Rahmat A, Othman F, Akim A. The C*entella asiatica* juice effects on DNA damage, apoptosis and gene expression in hepatocellular carcinoma (HCC). BMC Complement Altern Med 2014; 14:32.
42. Hussin M, Abdul-Hamid A, Mohamad S, Saari N, Ismail M, Bejo MH. Protective effect of *Centella asiatica* extract and powder on oxidative stress in rats. Food Chem 2007;100(2):535-41.
43. Idris NA, Nadzir MM. Antimicrobial activity of *Centella asiatica* on *Aspergillus niger* and *Bacillus subtilis*. Chem Eng Trans 2017; 56:1381-6.
44. Inamdar PK, Yeole RD, Ghogare AB, De Souza NJ. Determination of biologically active constituents in *Centella asiatica*. J Chromatogr A 1996;742(1-2):127-30.
45. J. Barnes, L. A. Anderson, and J. D. Phillipson, Herbal Medicines, London, UK: Pharmaceutical Press, 2007.
46. James JT, Dubery IA. Pentacyclic triterpenoids from the medicinal herb, *Centella asiatica* (L.) Urban. Molecules 2009;14(10):3922-41.
47. Jayashree G, Kurup Muraleedhara GK, Sudarslal S, Jacob VB. Anti-oxidant activity of *Centella asiatica* on lymphoma-bearing mice. Fitoterapia 2003;74(5):431-4.
48. Jeong BS, Kim YC, Lee ES. Modification of C2, 3, 23, 28 functional groups on asiatic acid and evaluation of hepatoprotective effects. Bull Korean Chem Soc 2007;28(6):977-82.
49. Joshi K, Chaturvedi P. Therapeutic efficiency of *Centella asiatica* (L.) Urb. An underutilized green leafy vegetable: an overview. International Journal of Pharma and Bio Sciences. 2013 ;4(1):135-49.
50. Kabir AU, Samad MB, D'Costa NM, Akhter F, Ahmed A, Hannan JM. Anti-hyperglycemic activity of *Centella asiatica* is partly mediated by carbohydrase inhibition and glucose-fiber binding. BMC Complement Altern Med 2014; 14:31.
51. Kalshetty P, Aswar U, Bodhankar S, Sinnathambi A, Mohan V, Thakurdesai P. Antidepressant effects of standardized extract of *Centella asiatica* L in olfactory bulbectomy model. Biomed Aging Pathol 2012;2(2):48-53.
52. Kim KB, Kim K, Bae S, Choi Y, Cha HJ, Kim SY, et al. MicroRNA-1290 promotes asiatic acid-induced apoptosis by decreasing BCL2 protein level in A549 non-small cell lung carcinoma cells. Oncol Rep 2014;32(3):1029-36.
53. Kumar A, Dogra S, Prakash A. Neuroprotective effects of *Centella asiatica* against intracerebroventricular colchicine-induced cognitive impairment and oxidative stress. Int J Alzheimers Dis 2009;2009. pii: 972178.
54. Kumar A, Prakash A, Dogra S. *Centella asiatica* attenuates D-galactose-induced cognitive impairment, oxidative and mitochondrial dysfunction in mice. Int J Alzheimers Dis 2011; 2011:347569.
55. Kwon KJ, Bae S, Kim K, An IS, Ahn KJ, An S, et al. Asiaticoside, a component of *Centella asiatica*, inhibits melanogenesis in B16F10 mouse melanoma. Mol Med Rep 2014;10(1):503-7.
56. Lin X, Huang R, Zhang S, Wei L, Zhuo L, Wu X, et al. Beneficial effects of asiaticoside on cognitive deficits in senescence-accelerated mice. Fitoterapia 2013;87(10):69-77.
57. Liu J, He T, Lu Q, Shang J, Sun H, Zhang L. Asiatic acid preserves beta cell mass and mitigates hyperglycemia in streptozocin-induced diabetic rats. Diabetes Metab Res Rev 2010;26(6):448-54.
58. Lopez-Lopez G, Moreno L, Cogolludo A, Galisteo M, Ibarra M, Duarte J, Lodi F, Tamargo J, Perez-Vizcaino F (2004) Nitric oxide (NO) scavenging and NO protecting effects of quercetin and their biological significance in vascular smooth muscle. Mol Pharmacol 65(4):851–859.
59. Maulidiani, Abas F, Khatib A, Perumal V, Suppaiah V, Ismail A, et al. Metabolic alteration in obese diabetes rats upon treatment with Centella asiatica extract. J Ethnopharmacol 2016; 180:60-9.
60. N. J. Chong and Z. Aziz, "A systematic review of the efficacy of *Centella asiatica* for improvement of the signs and symptoms of chronic venous insufficiency," Evidence-Based Complementary and Alternative Medicine, 2013.
61. Nasir MN, Habsah M, Zamzuri I, Rammes G, Hasnan J, Abdullah J. Effects of asiatic acid on passive and active avoidance task in male Spraque - Dawley rats. J Ethnopharmacol 2011;134(2):203-9.
62. Orhan IE, Atasu E, Senol FS, Ozturk N, Demirci B, Das K, et al. Comparative studies on Turkish and Indian *Centella asiatica* (L.) Urban (gotu kola) samples for their enzyme inhibitory and antioxidant effects and phytochemical characterization. Ind Crops Prod 2013; 47:316-322.
63. Orhan IE. *Centella asiatica* (L.) Urban: From traditional medicine to modern medicine with neuroprotective potential. Evid Based Complement Altern Med 2012; 2012:946259.
64. Oyedeji OA, Afolayan AJ. Chemical composition and antibacterial activity of the essential oil of *Centella asiatica*. Growing in South Africa. Pharma Biol 2005;43(3):249-52.
65. Oyenihi AB, Chegou NN, Oguntibeju OO, Masola B. *Centella asiatica* enhances hepatic antioxidant status and regulates hepatic inflammatory cytokines in Type 2 diabetic rats. Pharm Biol 2017;55(1):1671-8.
66. P. Bhandari, N. Kumar, A. P. Gupta, B. Singh, and V. K. Kaul, "A rapid RP-HPTLC densitometry method for simultaneous determination of major flavonoids in important medicinal plants," Journal of Separation Science, vol. 30, no. 13, pp. 2092–2096, 2007.
67. Park BC, Bosire KO, Lee ES, Lee YS, Kim JA. Asiatic acid induces apoptosis in SK-MEL-2 human melanoma cells. Cancer Lett 2005;218(1):81-90.
68. Pitinidhipat N. Antibacterial activity of *Chrysanthemum indicum*, *Centella asiatica* and *Andrographis paniculata* against *Bacillus cereus* and *Listeria monocytogenes* under osmotic stress. AUJT 2015;15(4):239-45.
69. Pittella F, Dutra RC, Junior DD, Lopes MT, Barbosa NR. Antioxidant and cytotoxic activities of *Centella asiatica* (L) Urb. Int J Mol Sci 2009;10(10):3713-21.
70. Ponnusamy K, Mohan M, Nagaraja HS. Protective antioxidant effect of *Centella asiatica* bioflavonoids on lead acetate induced neurotoxicity. Med J Malaysia 2008;63 Suppl A:102.
71. Prakash A, Kumar A. Mitoprotective effect of *Centella asiatica* against aluminum-induced neurotoxicity in rats: Possible relevance to its anti-oxidant and anti-apoptosis mechanism. Neurol Sci 2013;34(8):1403-9.
72. Prakash V. Terpenoids as source of anti-inflammatory compounds. Asian J Pharm Clin Res 2017;10(3):68-76.

73. Rahman MM, Sayeed MS, Haque MA, Hassan MM, Islam SA. Phytochemical screening, antioxidant, anti-Alzheimer and anti-diabetic activities of *Centella asiatica*. J Nat Prod Plant Resour 2012;2(4):504-11.
74. Rahman S, Jamal MM, Parvin A, Mahfuz-Al-Mamun M, Islam MR. Antidiabetic activity of *Centella asiatica* (L.) urbana in alloxan induced Type 1 diabetic model rats. J Biosci 2012; 19:23-7.
75. Rajalingam D, Varadharajan R, Palani S. Evaluation of hepatoprotective and antioxidant effect of *Combretum albidum* G. don against CCl_4 induced hepatotoxicity in rats. Int J Pharm Sci 2016;8(9):218-23.
76. Randriamampionona D, Diallo B, Rakotoniriana F, Rabemanantso C, Cheuk K, Corbisier AM, et al. Comparative analysis of active constituents in *Centella asiatica* samples from Madagascar: Application for ex situ conservation and clonal propagation. Fitoterapia 2007;78(7-8):482-9.
77. Raza SA, Adnan A, Qureshi F. Comparison of antioxidant activity of essential oil of Centella asiatica and Butylatedhydroxyanisole in sunflower oil at ambient conditions. Biharean Biol 2009;3(1):71-5.
78. Roy DC, Barman SK, Shaik MM. Current updates on *Centella asiatica*: Phytochemistry, pharmacology and traditional uses. Med Plant Res 2013;3(4):70-7.
79. S. S. Jamil, Q. Nizami, and M. Salam, "*Centella asiatica* L. Urban; a review," Natural Product Radiance, vol. 6, no. 2, pp. 158–170, 2007.
80. Saha S, Guria T, Singha T, Maity TK. Evaluation of analgesic and anti-inflammatory activity of chloroform and methanol extracts of *Centella asiatica* Linn. ISRN Pharmacol 2013; 2013:789613.
81. Sekar T, Ayyanar M, Pillai YJ. Phytochemical screening and antibacterial activity of leaf and callus extracts of Centella asiatica. Bangladesh J Pharmacol 2011;6(1):55-60.
82. Sharma PV. (1981) Dravyaguna Vigyana, vol II and V, Press Chaukhambha Bharati Academy: Varanasi.
83. Shetty BS, Udupa SL, Udupa AL, Somayaji SN. Effect of Centella asiatica L (Umbelliferae) on normal and dexamethasone-suppressed wound healing in Wistar Albino rats. Int J Low Extrem Wounds 2006;5(3):137-43.
84. Shinomol GK, Muralidhara (2008) Prophylactic neuroprotective property of Centella asiatica against 3-nitropropionic acid induced oxidative stress and mitochondrial dysfunctions in brain regions of prepubertal mice. Neurotoxicology 29(6):948–957.
85. Siddiqui BS, Aslam H, Ali ST, Khan S, Begum S. Chemical constituents of *Centella asiatica*. J Asian Nat Prod Res 2007;9(3-5):407-14.
86. Sirichoat A, Chaijaroonkhanarak W, Prachaney P, Pannangrong W, Leksomboon R, Chaichun A, et al. Effects of asiatic Acid on spatial working memory and cell proliferation in the adult rat hippocampus. Nutrients 2015; 7:8413-23.
87. Somboonwong J, Kankaisre M, Tantisira B, Tantisira MH. Wound healing activities of different extracts of *Centella asiatica* in incision and burn wound models: An experimental animal study. BMC Complement Altern Med 2012; 12:103.
88. Somchit MN, Sulaiman MR, Zuraini A, Samsuddin L, Somchit N, Israf DA, et al. Antinociceptive and antiinflammatory effects of Centella asiatica. Indian J Pharmacol 2004;36(6):377.
89. Suguna L, Sivakumar P, Chandrakasan G. Effects of Centella asiatica extract on dermal wound healing in rats. Indian J Exp Biol 1996;34(12):1208-11.
90. Sultan RA, Mahmood SB, Azhar I, Ahmed SW, Mahmood ZA. Biological activities assessment of *Centella asiatica* (Linn.). J Herbs Spices Med Plants 2014;20(3):319-27.
91. Sultana N, Saify ZS. Naturally occurring and synthetic agents as potential anti-inflammatory and immunomodulants. Antiinflamm Antiallergy Agents Med Chem 2012;11(1):3-19.
92. Supkamonseni N, Thinkratok A, Meksuriyen D, Srisawat R. Hypolipidemic and hypoglycemic effects of *Centella asiatica* (L.) extract in vitro and *in-vivo*. Indian J Exp Biol 2014;52(10):965-71.
93. Tang LX, He RH, Yang G, Tan JJ, Zhou L, Meng XM, et al. Asiatic acid inhibits liver fibrosis by blocking TGF-beta/Smad signaling in vivo and in vitro. PLoS One 2012;7(2): e31350.
94. Taylor J. P., Brown R. H. Jr and Cleveland D. W. (2016). Decoding ALS: from genes to mechanism. Nature 539, 197-206.
95. Thomas TN, Thomas PM. Patent Application No. 14/848,372. U.S; 2015.
96. Umka Welbat J, Sirichoat A, Chaijaroonkhanarak W, Prachaney P, Pannangrong W, Pakdeechote P, et al. Asiatic acid prevents the deleterious effects of valproic acid on cognition and hippocampal cell proliferation and survival. Nutrients 2016;8(5). pii: E303.
97. USDA N. The PLANTS Database (http://plants. usda. gov). National Plant Data Center, Baton Rouge. (Last accessed on December 10, 2021).
98. Veerendra Kumar MH, Gupta YK. Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. Clin Exp Pharmacol Physiol 2003;30(5-6):336-42.
99. Wang L, Xu J, Zhao C, Zhao L, Feng B. Antiproliferative, cell-cycle dysregulation effects of novel asiatic acid derivatives on human non-small cell lung cancer cells. Chem Pharm Bull (Tokyo) 2013;61(10):1015-23.
100. Wang X, Lu Q, Yu DS, Chen YP, Shang J, Zhang LY, et al. Asiatic acid mitigates hyperglycemia and reduces islet fibrosis in Goto-Kakizaki rat, a spontaneous Type 2 diabetic animal model. Chin J Nat Med 2015;13(7):529-34.
101. Wattanathorn J, Mator L, Muchimapura S, Tongun T, Pasuriwong O, Piyawatkul N, et al. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of *Centella asiatica*. J Ethnopharmacol 2008;116(2):325-2.
102. Wu T, Geng J, Guo W, Gao J, Zhu X. Asiatic acid inhibits lung cancer cell growth in vitro and in vivo by destroying mitochondria. Acta Pharm Sin B 2017;7(1):65-72.
103. Wyss-Coray T. (2016). Ageing, neurodegeneration and brain rejuvenation. Nature 539, 180-186.
104. Xu Y, Cao Z, Khan I, Luo Y. Gotu Kola (*Centella asiatica*) extract enhances phosphorylation of cyclic AMP response element binding protein in neuroblastoma cells expressing amyloid beta peptide. J Alzheimers Dis 2008;13(3):341-9.
105. Yao CH, Yeh JY, Chen YS, Li MH, Huang CH. Wound-healing effect of electrospun gelatin nanofibres containing *Centella asiatica* extract in a rat model. J Tissue Eng Regen Med 2017;11(3):905-15.

106. Yu QL, Duan HQ, Gao WY, Takaishi Y. A new triterpene and a saponin from *Centella asiatica*. Chin Chem Lett 2007;18(1):62-4.
107. Zaidan MR, Noor Rain A, Badrul AR, Adlin A, Norazah A, Zakiah I. In-vitro screening of five local medicinal plants for antibacterial activity using disc diffusion method. Trop Biomed 2005;22(2):165-70.
108. Zhang J, Ai L, Lv T, Jiang X, Liu F. Asiatic acid, a triterpene, inhibits cell proliferation through regulating the expression of focal adhesion kinase in multiple myeloma cells. Oncol Lett 2013;6(6):1762-6.