# Introduction

Centella asiatica (L.) Urban (C. asiatica) is a brown and green leafy plant of the parsley family that grows in, or nearby, water [1].C. asiatica flowers bloom between August and September and are light purple. The plant has an aroma of tobacco leaves. The leafstalk grows between 5 and 15 cm high, starting from a base, and branching to individual leaf clusters that resemble a rose.

The leaves are greenish-yellow in color and edible. The leafstalk is very slender with few scattered hairs [2]. C. asiatica is known in many parts of the world, as included in Table 1.

C. asiatica is indigenous to Southeast Asia, China and India and also grows in Columbia, Venezuela and the southeastern region of the United States [2,3]. C. asiatica thrives in moist conditions and shaded areas at an altitude between 0 and 2500 meters above sea level [2].

Referenced in classical Indian Ayurveda literature, medicinal uses of C. asiatica, include treating abnormal skin texture and skin conditions, and enhancing memory cognition. It is often referred to as a cognitive enhancer [4]. Dating back to its first use in approximately 1700 AD, traditional uses of C. asiatica included treatment for leprosy, lupus, ulcers, diarrhea, fever, eczema and psoriasis. The first clinical study is referenced from 1945 [4]. Treatment solutions were shared via word of mouth and shared as folk remedies.

C. asiatica has recently been introduced in modern medicine as an alternative remedial solution and has been included in clinical studies testing memory in relation to reaction time and Alzheimer's disease, and as a topical remedy for skin ulcers and wounds. In vitro and in vivo studies have found C. asiatica improves memory and cognition in rats exposed to maze tests, but that the plant extract does not influence motor functioning skills. More clinical studies must be done to determine the ways in which C. asiatica influences and works with other compounds.

Conventional uses of C. asiatica include Centellase, Madecassol and Emdecassol. Centellase is made up of C. asiatica, madecassic acid, asiatic acid and asiaticosides and is available in tablet, ointment and powder form [2]. Madecassol consists of asiaticoside, asiatic acid, madecassic acid and madasiatic acid and is available as an ointment or cream, or powder [2]. Emdecassol is comprised of Hydrocotyle asiatica herb, which consists of a variety of asiaticoside acid and triterpenoid acid [2]. The surface region of the leaves are extracted, dried and used for medicinal purposes. The asiatica species is used in commercial drugs and is available in Germany [2].

This comprehensive research article reviews clinical tests that determine the therapeutic and pharmacodynamics of C. asiatica and its therapeutic and anti-degenerative potential as a therapeutic agent for Alzheimer's disease, memory, diabetes mellitus, wound healing, venous insufficiency and varicose veins, and anti-inflammation.

## Chemical Composition

C. asiatica extracts include flavonoids and terpenes derived from Phenylpropane and acetate [2]. Triterpene acids and their sugar esters, including asiatic acid, madecassic acid and asiaticosides: asiaticoside A and asiaticoside B, are of therapeutic significance [2]. The high phenolic contents of C. asiatica make it a high producer of antioxidant activities [5]. C. asiatica may contain up to 8% of triterpenic acid sugar esters depending on the origin of the plant [2].

## Pharmacodynamics

Pharmacological studies have found C. asiatica extract to regulate central nervous system activity and also protect against changes in behavior and performance caused by radiation, although none have been reported in literature [6]. Studies have also shown C. asiatica to be more effective in preventing or reducing nausea and vomiting for patients experiencing radiotherapy treatment, as proven on radiation-induced male rats. In addition to the remedial functions of C. asiatica, the plant also has central nervous depressant activity and has proven cognitive advancements in various pharmacological studies, including improved maze learning in rats. Maze test conducted on rats examines the neurotropic of C. asiatica effect during postnatal brain development, but there are little to no

studies done of the effect of the plant extract during early developmental stages [7].

## Anxiolytic Properties

C. asiatica has a historic reputation for reducing anxiety. Waijeweera et al. tested C. asiatica on anxiety levels in rats during the elevated plus maze, open field test, social interaction test, locomotor activity, Vogel test and novel environment test and found that anxiolytic activity may be cause of triterpene heavy components in extracts of C. asiatica. Although other active compounds may contribute to important plant activity effected by, or linked with asiaticoside, asiaticoside is the most active and most dominant triterpene [8].

## Antioxidant Activity

Oxidative stress inflicts physical function in age. Antioxidants curb age-related physical and cognitive declines and also contribute to a positive influence in psychological capacity [9]. To determine the positive influence and antioxidant functions of C. asiatica, Mato et al. tested the positive influence and antioxidant functions of C. asiatica on physical ability, physical satisfaction and emotional wellness and outlook in healthy elderly volunteers [9]. Mato et al. defined health as a "dynamic state of well-being characterized by a physical, mental and social potential affected by "health" [9]. C. asiatica was a candidate herbal remedy for improved physicality in healthy elderly because of its antioxidant compounds.

Mato et al. determined C. asiatica as an herbal remedy candidate for improved physicality in healthy elderly because of its antioxidant compounds. The improvement of physical health and quality of life influenced by C. asiatica was tested on elderly volunteers for two months.

Volunteers participated in various strength tests under the controlled administration of C. asiatica (doses of 500 and 750 mg/daily). Strength tests determined the improved strength of the leg, specifically the thigh, ankle, foot and hip. After two months of tests and doses of C. asiatica, Mato et al. found that leg, thigh, ankle, foot and hip strength increased, determining that C. asiatica can improve quality of life and physical capacities.

## Alzheimer's Disease

In various studies testing cognitive improvements of rats and standard shuttle box, step-through paradigm, elevated plus maze and passive avoidance tests, C. asiatica improved learning and memory [10]. When aqueous extracts of C. asiatica at doses of 100-300 mg/kg per day were distributed to newborn mice from 15 days old to 30 days old, learning and spatial memory were improved without influencing motor functioning skills [10]. Soumyanath et al. reported that doses of C. asiatica influenced the cell nerves of the pyramidal cells in the prefrontal cortex, the hippocampus, and other areas, in newborn and adult mice and rats [10]. Soumyanath et al. suggest that results from these studies presents aqueous extract of C. asiatica as lowering the degenerative impairments of memory, learning and aging in relation to Alzheimer's disease [10].

Soumyanath et al. tested the effect of aqueous extract C. asiatica on behavioral loss in the Tg2576 transgenic mouse, most commonly used for Alzheimer's disease testing. To test characteristics similar to Alzheimer's disease, the mutant human amyloid precursor protein (APP) was injected in each mouse. APP produces cortical β-amyloid (Aβ) plaques similar to Alzheimer's disease pathology [10]. Fifteen Tg2576 mice and twenty wild-type twenty-month-old female mice organized according to genotype. Half of each genotype group was given C. asiatica in drinking water (2 mg/mL) and water bottles were changed every other day. Spatial memory impairment in Tg2576 mice progressed with C. asiatica treatment. The progression was correlated with the appearance of Aβ plaques [10].

Although few studies have been performed on humans, Soumyanath et al. found that C. asiatica improved the mental capabilities of 30 mentally retarded children. Thirty children between the ages of 7-18 were administered 500 mg of the dried herb/daily for three months. It was found that C. asiatica improved mental capabilities [10].

## Memory: Learning and Cognition

The positive impact of C. asiatica on memory, specifically learning and cognition, were found in a study by Kumar et al. Aqueous extract of the whole plant was administered to rats participating in various shuttle boxes and step

through paradigms. It was found that C. asiatica doses lowered the number of avoidance response. This suggested that C. asiatica as a mechanism for improving learning and memory.

Examining C. asiatica extracts on various brain markers, including malondialdehyde (MDA), glutathione, superoxide dismutase (SOD) and catalase, Kumar et al. found improved memory and cognitive ability during various cognitive tests with administered doses of the aqueous extract of the whole plant. Either 100, 200 or 300 mg/kg doses were administered for 14 days. Accordingly, increased quantities of the aqueous extract correlated to improved cognition and memory in each iteration of the memory tests, increasing the avoidance response in shuttle box and prolonged the step through latency in step through apparatus. Transfer latency (TL) and step down latency in step down apparatus in elevated plus maze were increased with two doses of 200 and 300 mg/kg of aqueous C. asiatica extract [11]. Aqueous extract of C. asiatica at 200 and 300 mg/kg doses lowered the malondialdehyde (MDA) levels in the brain. There was no change in the levels of superoxide dismutase (SOD) [11].

Kumar et al. learned that aqueous extract of the whole plant of C. asiatica enhanced memory retention and learning and reduced the lipid peroxidation and growth of endogenous antioxidant enzymes in brain [11]. Avoidance responses in step through latency in the step through apparatus test were lower because of the administered doses of C. asiatica [11].

### Cognition and Memory in Elderly

To better understand the neurochemical and behavioral changes that occur in aging adults, Wattanathorn et al. proposed a new method of stabilizing the degenerative cognitive function of elderly adults by testing the effect of C. asiatica on attention, memory, locomotor function and reaction time. The pilot study was held for 8-weeks as a double-blinded, placebo-controlled, randomized trial with twenty-eight healthy elderly volunteers between the ages of 62-65 (four male and twenty-four female). Participants were administered with either a capsule of placebo or an extract of C. asiatica at doses from 250, 500 and 750 mg, once per day for two months [4].

After one to two months, Wattanathorn et al. found that high doses of C. asiatica extract actively improved “calmness and alertness,” memory and improved the response time of both numeric working memory and spatial memory [4].

### Diabetes Mellitus

In an effort to combat global rise of diabetes mellitus, Ramachandran et al. suggest that plant-based medicine may compliment the tailored diet, physical exercise, oral medications and insulin therapy of diabetic patients. C. asiatica is a strong candidate for alleviating diabetic symptoms, and perhaps controlling the increase of diabetes mellitus, because of its various compounds and functions.

Ramachandran et al. explored the various compounds and functions of triterpenoid compounds, hepatoprotective functions, anti-inflammatory functions, and antioxidant properties of C. asiatica on rats. Rats were organized into seven groups of six rats and administered a mixture of asiatic acid, dissolved in 5% DMSO, and glibenclamide, dissolved in water. The water mixture was administered for 45 days via an intragastric tube [12].

The mixture of asiatic acid and glibenclamide blocked the development of glycosylated hemoglobin which caused an increase in the total amount of hemoglobin in diabetic rats. Ramachandran et al. suggest the increase in hemoglobin as a result of improved glycemic control from asiatic acid [12].

Ramachandran et al. report that previous studies have found that the inflation of gluconeogenic enzymes decreased when treated with other triterpenoids, including ursolic acid and 18β-glycyrrhetinic acid [12]. Either the metabolism or inhibition of glycolysis and gluconeogenesis maintained the activities of triterpenoids when rats were treated with C. asiatica [12].

### Wound Healing and Skin Lesions

Terpenes are the most active group of compounds located in C. asiatica. The largest triterpene glycoside is asiaticoside, which promotes wound healing and can augment the antioxidant levels at an early stage of wound

healing [8].

## Diabetic Ulcers

To better understand the healing properties of C. asiatica on diabetic foot ulcers, Kuo et al. conducted a single-center, randomized, controlled, open-label study on 24 Type 1 or Type 2 diabetes mellitus patients with Wagner grade 3 foot ulcers postsurgery. Participants for the study had either Type 1 or Type 2 diabetes mellitus, were at least 20 years or older with Wagner grade 3 foot ulcers post-surgery. According to the Wagner classification system, Wagner grade 3 is defined as a "deep ulcer involving osteitis, abscess, or osteomyelitis" [13] and describes patients with poor nutritional status (albumin <3 g/dL), poor diabetic control (HbAlc >10%), anemia (hemoglobin <10 g/dL), and leukocyte counts <1,000/cu mm were excluded [13].

Twenty-four screened participants were enrolled in the study and randomly organized in two groups of twelve: a WH-1 cream group and a hydrocolloid fiber dressing group. Twelve patients applied topical cream WH-1 over their ulcer twice a day for two weeks. Patients were instructed to apply a thin and even layer of the topical cream to completely cover the ulcer and surrounding area [13].

Kuo et al. found no convincing difference, statistically or otherwise, when comparing percent changes in wound size and improvements of botanical cream containing P. amboinicus and C. asiatica against the results of hydrocollpoid fiber wound dressing applied topically to diabetic foot ulcers. Kuo et al. reported no major benefits of either WH-1 cream or hydrocolloid fiber dressing when comparing results and determined P. amboinicus and C. asiatica cream to be a safe and effective alternate to hydrocolloid fiber wound dressing without significant difference in effectiveness [13].

## Venous Insufficiency and Varicose Veins

Venous insufficiency is a result of stagnated blood in leg veins that causes fluid to leak out of the blood vessels as the blood vessels lose their elasticity. A few studies have shown C. asiatica to assist in abscess reduction and increase blood flow to reduce symptoms and alleviate conditions of venous insufficiency [1].

To test the biochemical components of C. asiatica in patients with varicose veins, Arpaia et al. supervised controlled doses of C. asiatica to 20 patients with varicose veins in the leg and observed results for three months. By examining serum levels of uric acid lysosomal enzyme activity in relation to the mucopolysaccharide metabolism, Arpaia et al. set an elevated baseline serum of uric acid and elevated lysosomal enzymes as a test point. After C. asiatica treatment, Arpaia et al. found the reduced uric acid serum levels and lysosomal enzymes [2].

## Chronic Venous Insufficiency

Chronic venous insufficiency (CVI) is a condition that makes it difficult for the veins in the legs and lower extremities to send blood back to the heart. CVI can be caused from abnormalities of the venous wall and valves [14]. Aminaftone and calcium dobesilate drugs have been used as part of treatment therapies for CVI but little evidence is provided to determine the degree of effectiveness. Flavonoids, saponosides and diosmin are compounds in C. asiatica that have been assessed for treating onset symptoms of CVI and venous microangiopathy [14]. C. asiatica is a candidate for reducing signs and symptoms of CVI and microangiopathy in the lower extremities because of its triterpenes contents. Triterpenes assist with anti-inflammation, as seen in various animal studies [14].

Chong et al. conducted a comprehensive scientific literature review to determine the ways in which C. asiatica may improve CVI and CVI symptoms. The comprehensive scientific literature review included studies that recruited patients with venous insufficiency or venous hypertension, because many of the randomized controlled trials did not use specific diagnostic classification of CVI [14]. Short-term effects of the plant compounds have been found effective, but long-term effects are inconclusive. Short-term effects include reducing symptoms of pain and oedema as related to CVI [14]. Other symptoms of CVI include feelings of heaviness, cramps, pains, leg discomfort, oedema, and skin changes [14].

Patients treated with C. asiatica showed significant improvement in CVI signs including oedema, pain and heaviness.

Chong et al. suggest C. asiatica as a possible remedy for CVI symptoms with more studies with clearer data and reporting [14].

## Anti-inflammation

The overproduction of free radicals increases a risk of oxidative damage to biomolecules, lipids, proteins and DNA [15]. Oxidative damage can cause chronic diseases, including degenerative diseases, diabetes mellitus, cancer and atherosclerosis. Natural antioxidants and the intake of natural antioxidants, as found in fruits, vegetables and medicinal herbs, contain free radical scavenging molecules that can help reduce the risk of degenerative diseases, cardiovascular disease and diabetes mellitus [15].

Reduce Skin Aging

Well-known bioactive agents of C. asiatica are polyacetylenes, triterpenoid saponins (asiaticoside and madecassoside) and sapoogenins [16]. While producing these compounds via vitro culture, researchers found low amounts of these agents and high amounts of caffeoyl derivatives, specifically, 3,5-O-dicaffeoyl- 4-omalonilquinic acid. This type of acid is significant because it can absorb UV light from a range of 300 and 330 nm, lowers the progression of skin ageing, protects skin from UV damage and suppresses collagen breakdown [16].

A study by Gohil et al. found that C. asiatica acted on the connective tissues of the vascular wall. In conditions of hypertensive microangiopathy and venous insufficiency, C. asiatica can improve microcirculatory parameters by lowering capillary filtration, making C. asiatica a candidate for reducing the appearance of skin ageing [17].

## Safety and Dosage

While using suggested doses of C. asiatica extract will not cause serious side effects, using large amounts of C. asiatica for topical use of C. asiatica may cause skin allergies and burning sensations, headache, upset stomach, nausea, dizziness and drowsiness. Fresh C. asiatica may cause a skin rash [17].

Taking very large amounts of C. asiatica can be the source of headaches and unconsciousness. Taking C. asiatica for a long period of time may make it difficult for women to become pregnant and may cause spontaneous abortion for pregnant women [17].

Individuals taking sleep aides should not consume C. asiatica in high doses as it is a sedative [17].

## Drugs that Affect the Liver

Individuals taking liver medication should be cautious when taking C. asiatica as the plant contains compounds and extracts that may affect the prescription medicine and taking it with prescription medicine may cause serious liver damage [1].

## Cholesterol-lowering Drugs (Including Statins)

When tested in various animal studies, C. asiatica increased cholesterol levels and may also do the same in humans, although no conclusive data can support this claim [1].

## Diabetes Mellitus Medication

When tested in various animal studies, C. asiatica increased blood sugar levels. Individuals with diabetes mellitus should consult their doctor before taking C. asiatica [1].

## Diuretics (Water Pills)

C. asiatica can serve a diuretic and individuals should be aware of the dangers of losing large amounts of fluids if diuretic symptoms occur [1].

## Sedatives

C. asiatica serves as an herbal sedative and may interfere with other medications or remedies that alleviate anxiety or insomnia [1].

About 600 mg of dried C. asiatica or infused C. asiatica in a singledose capsule is considered a normal dose. A single-dose capsule ranges between 300 mg and 680 mg which can be taken up to three times a day [17].

To enjoy C. asiatica leaves as a tea, add 1-2 teaspoons of dried leaves to 2/3 cups of boiling water. Steep for

approximately 10-15 minutes [17].

Modern herbal medicine uses up to 100% total saponins (triterpenoid). Individuals can consume 60 mg once or twice daily [17].

## Discussion

Clinical and preclinical studies found oral and treatment of controlled doses of C. asiatica to assist with antioxidant production and alleviate slow wound healing. In vitro and in vivo studies found that C. asiatica can alleviate common side effects of radiotherapy, including nausea and vomiting. A study by Rao et al. found that rat models exposed to radiation experienced reduced symptoms of nausea and vomiting and exposure to C. asiatica also improved the life span [7].

In a test by Waijeweera et al., C. asiatica reduced levels of anxiety in rat models exposed to novel experiences. During an elevated plus maze and open field test, high anxiolytic activity may have been causation of triterpene heavy components in extracts of C. asiatica. This was left inconclusive as other compounds may have influenced asiaticoside [8].

The high concentration of antioxidant compounds in C. asiatica makes it a strong candidate herbal remedy for improved physicality in healthy elderly, as found in a test on elderly adult volunteers for two months. Volunteers were asked to perform a series of strength tests while taking controlled doses of the plant. Physical strength was improved as the time it took to complete the tests was reduced and feelings of vitality were increased [9].

Studies determining the influence of the plant on Alzheimer's disease a memory and cognition yielded successful results. When aqueous extracts of C. asiatica at doses of 100-300 mg/kg per day were distributed to newborn mice from 15 days old to 30 days old, learning and spatial memory were improved without influencing motor functioning skills [10]. Soumyanath et al. reported that doses of C. asiatica influenced the cell nerves of the pyramidal cells in the prefrontal cortex, the hippocampus, and other areas, in newborn and adult mice and rats [10]. Soumyanath et al. suggest that results from these studies present aqueous extract of C. asiatica as lowering the degenerative impairments of memory, learning and aging in relation to Alzheimer's disease [10].

The most significant test we reviewed examined C. asiatica on various brain markers. Kumar et al. found improved memory and cognitive ability during various cognitive tests with administered doses of the aqueous extract of the whole plant. Either 100, 200 or 300 mg/kg doses were administered for 14 days. Accordingly, increased quantities of the aqueous extract correlated to improved cognition and memory in each iteration of the memory tests, increasing the avoidance response in shuttle box and prolonged the step through latency in step through apparatus. C. asiatica is a strong candidate for alleviating diabetic symptoms, and perhaps controlling the increase of diabetes mellitus, because of its various compounds and functions.

To better understand the compounds and functions of triterpenoid compounds, hepatoprotective functions, anti-inflammatory functions, and antioxidant properties of C. asiatica, a water mixture was administered to rats via intragastric tube for 45 days [12]. The water mixture was made up of asiatic acid, dissolved in 5% DMSO, and glibenclamide, dissolved in water. The water mixture successfully blocked the development of glycosylated hemoglobin [12]. Either the metabolism or inhibition of glycolysis and gluconeogenesis maintained the activities of triterpenoids when rats were treated with C. asiatica [12]

Terpenes are the most active group of compounds located in C. asiatica. The largest triterpene glycoside is asiaticoside, which promotes wound healing and can augment the antioxidant levels at an early stage of wound healing [8]. C. asiatica may be a useful ingredient in topical skin cream or ointment to treat minor burns and psoriasis, prevent or reduce the appearance of stretch marks, and prevent or reduce the appearance of surgery scars [1] (Figure 1).

## Conclusion

Plants have been used as herbal remedies for decades, and researched as alternative pharmaceutical solutions, for

years. This review article highlights the therapeutic and medicinal capacities of C. asiatica and its potential as a therapeutic agent for Alzheimer's disease, memory, diabetes mellitus, wound healing, venous insufficiency and varicose veins, and anti-inflammation. Oral use of C. asiatica and In vitro studies have improved memory and cognition, stabilizing diabetic symptoms, aid topical wounds and alleviate swelling. In vitro studies in animals have found C. asiatica to improve memory and increase reaction time, and assist with the wound-healing process. Dose-dependent amounts of aqueous extract of C. asiatica also decrease the appearance of aging skin, collagen, and topical scars [2]. Authors suggest that with additional research, C. asiatica may be a leading candidate for treating degenerative diseases.