AN INSIGHT ON *CENTELLA ASIATICA* LINN. : A REVIEW ON RECENT RESEARCH

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Summary

This review describes the morphology, microscopy, traditional and folklore uses, phyto-constituents, pharmacological reports, clinical pharmacology of *Centella asiatica* Linn. Flavonoids, glycosides, alkaloids, volatile constituents, *etc.* have been reported as the major phyto-constituents of the plant. The plant has been used for curing various ailments, hence acts as antiulcer, gastro protective, hepatoprotective, cardio protective, *etc.,* the most important being neuroprotective property. The pharmacological activities performed on the plant have been focused. The antidiabetic property of the plant has been highlighted with a view to explore, isolate and identify the medicinally important phyto-constituents responsible for it, which could be utilized to alleviate the disease affecting the mankind.

Key words: *Centella asiatica* Linn.; neuroprotective; phytochemistry; pharmacology; antidiabetic

Introduction

Centella or Indian Pennywort, *Centella asiatica* Linn., Urban synonyms *Hydrocotyle asiatica* Linn. belonging to the family Apiaceae is shown in Fig 1. The herb is known as Brahmi in Unani medicine, Mandookaparni in Ayurveda and Gotu Kola in the western world. In India, the plant was earlier confused for *Bacopa monnieri* Wettst., as both were sold in the market by the name 'Brahmi'. However, later on the controversy has been resolved and it was confirmed that Brahmi is *Bacopa monnieri* and Mandookaparni is *Centella asiatica* Linn.(1). It is a medicinal plant that has probably been used since prehistoric times and has been reported for its excellent medicinal and cosmetic properties, thus becoming an important commercial plant. This plant has been listed as a drug in the Indian Herbal Pharmacopoeia, the German Homeopathic Pharmacopoeia (GHP), the European Pharmacopoeia, and the Pharmacopoeia of the People's Republic of China (2).

The plant has various vernacular names, Brahmamunduki (Bengali), Chokiora (Bihar), Karinga (Marathi), Vallari (Deccan), Barmi (Gujrati), Mandookaparni, Brahmi, (Hindi), Muttil (Malyalam), Batmaina (Meghalaya), Thalkudi (Oriya), Mandukparnika (Sanskrit), Hingotukola (Sinhalase), Babassa (Telugu), Thuni-mankun (Tripura), Brahmi (Urdu) (3, 4, 5,6).

Geographically, plant is indigenous to the warmer regions of both hemispheres including Africa, Australia, Cambodia, Central America, China, Indonesia, the Lao People's Democratic Republic, Madagascar, the Pacific Islands, South America, Thailand, Southern United States of America and Vietnam. It is especially abundant in the swampy areas of India, the Islamic Republic of Iran, Pakistan and Sri Lanka up to an altitude of approximately 700m (7, 8, 9, 10, 11, 12).

Morphological description of *Centella asiatica* Linn.

A slender trailing herb, rooting at the nodes, leaves are 1.3-6.3 cm in diameter, orbicular reniform, more or less cupped, entire, crenate or lobulate, glabrous, leaf stalks are 2-5 cm long, peduncle about 6 mm, no pedicels, small bracts, single umbel inflorescence, bearing 1-5 white or reddish sessile flowers; Fruit is small, compressed, 8 mm long, mericarps longer then broad, curved, rounded at top, 7-9 ridged, secondary ridges as prominent as the primary, reticulate between them, pericarp is thickened and seed is compressed laterally (Fig 2.) (7, 8).

Organoleptic properties
It is greyish green in colour; characteristic odour; slightly bitter but sweet in taste (7, 13).

Microscopic characteristics
Plant is grayish green with stomata (30 by 28 μm) on both surfaces of the leaf. Rubiaceous type, palisade cells differentiated into 2 layers of cells, spongy parenchyma of about 3 layers of cells with many intercellular spaces, some with crystals of calcium oxalate, midrib region shows 2 or 3 layers of parenchymatous cells without chloroplastids; petiole shows epidermis with thickened inner walls; collenchyma of 2 or 3 layers of cells; a broad zone of parenchyma; 7 vascular bundles within parenchymatous zone, 2 in projecting arms and 5 forming the central strand; vessels 15-23 μm in diameter. Some parenchymatous cells contain crystals of calcium oxalate. Fruits, epidermis of polygonal cells, trichomes similar to the leaves, sheets of elongated parquetry layer cells, bundles of narrow annular vessels, and parenchymatous cells contain single large prisms of calcium oxalate (7)**.**

Chemical composition of *Centella asiatica* Linn.

Secondary metabolites are natural products that often have an ecological role in regulating the interactions between plants and their environment. They can be defensive substances, such as phytoalexins and phytoanticipins, anti-feedants, attractants and pheromones (Hanson, 2003). The importance of plant secondary metabolites in medicine, agriculture and industry has led to numerous studies on the synthesis, biosynthesis and biological activity of these substances. It has been estimated that over 40% of medicines have their origins in these active natural products (15).

The plant is reported to contain numerous phtoconstituents (terpenes, glycosides, saponins, flavonoids, alkaloids,*etc.*) as secondary metabolites.

Terpenes

Volatile and Fatty oil

The plant fatty oil consists of glycerides of palmitic acid, stearic acid , lignoceric acid, oleic acid, linoleic acid and linolenic acid (1).

Triterpene acids

The plant contains asiatic acid, madasiatic acid (2 α, 3 β, 6 β- trihydroxyurs-12-en-oic add), madecassic acid (madegascanc acid-6-hydroxy asiatic acid), terminolic acid, brahmic acid (2 α, 3 β, 6 β, 23-tetrahydroxy-urs-12-en-28-oic acid), centic acid, centellic acid, indocentoic acid, isobrahmic acid, betulic acid, centoic acid, *etc*. The corresponding triterpene acids obtained on hydrolysis of the glycosides are indocentoic acid, brahmic acid, asiatic acid, thankunic acid and isothankunic acid (1, 2, 16, 17, 18, 19, 20).

Glycosides

Asiaticoside A, B, C, D, E and F, madecassoside, and centelloside are isolated from the plant. On hydrolysis, these glycosides yield the triterpene acids, asiatic acid, madegascaric acid (madecassic acid) and centellic acid. These acids, except the last one, are also present in free form in the plant. Samples of the Indian plant collected from different places showed the presence of indocentelloside, brahmoside, brahminoside, thankuniside and isothankuniside. Glycoside D^1 and glycoside E^1 have also been reported (1, 2, 16, 17, 18, 19, 20).

Saponins

Saponins are also main constituent of *Centella asiatica* Linn. Various saponins are reported from the different species such as *Centella* saponins A, B, C and D (20).

Flavonoids

Flavonoids, 3-glucosylquercetin, 3-g1ucosylkaempferol and 7-glucosylkaempferol have been isolated from the leaves (1, 20, 21).

Alkaloids

An alkaloid, Hydrocotylin ($C_{l2}H_{33}NO_8$), has been isolated from the dried plant (21).

Others

The plant is reported to contain Mesoinositol, quercetin, kaempferol, stigmasterol, β-sitosterol, centellose, campesterol, oligosaccharide, polyacetylenes, carotenoids, vitamin B and vitamin C. A bitter principle vellarine, pectic acid, tannins, sugars, inorganic acids and resin are also present. The plant also contains amino acids, *viz*. aspartic acid, glycine, glutamic acid, α-alanine and phenylalanine have also been documented in the plant.

The total ash contains chloride, sulphate, phosphate, iron, calcium, magnesium, sodium and potassium (1, 2, 17, 18, 19, 21, 22, 23).

Constituent elements

The list of simple elements of which plants are primarily constructed- carbon, oxygen, hydrogen, calcium, phosphorus, *etc*. is not different from similar lists for animals, fungi, or even bacteria. The fundamental atomic components of plants are the same as for all life, only the details of the way in which they are assembled, differ. It is explained in **Table 1**.

Pharmacological role of *Centella asiatica* Linn.

The plant is bitter, acrid, sweet, cooling, soporific, cardiotonic, nervine tonic, stomachic, carminative, antileprotic, diuretic and febrifuge. It is useful in vitiated conditions of pitta, insomnia, cardiac debility, epilepsy, hoarseness, asthma, bronchitis, hiccough, amentia, abdominal disorders, leprosy, strangury and fever. These leaves are useful in abdominal disorders due to dysentery in children (6).

Charaka includes this drug in his *Vayasthapana Varga*, the group of drugs that are capable of maintaining the youthful vigour and strength, 'Mandooka Parni' is also a 'Medhya' drug, which improves the receptive and retensive capacity of the mind. The whole plant is reported to be nervine and cardiotonic, capable of improving memory power, physical strength, voice, complexion and digestive power (24).

The plant acts on nervous system as memory enhancer, neuroprotective, antidepressant, transquilizer, sedative, anxiolytic, nerve regenerator. It also heals gastric ulcers. It is a cardioprotective and hepatoprotective plant. It promotes wound healing and shows significant antiageing, antitumour, antioxidant, immunomodulating property, *etc*. Some of the pharmacological activities of the plant are explained.

Nervous System

Memory enhancing

Aqueous extract of the herb showed significant effect on learning capacity and significantly decreased the levels of norepinephrine, dopamine and 5-HT and their metabolites in the brain (25). Syrup prepared from *Centella* and *Bacopa* showed significant effect on learning ability of albino mice (26). Aqueous extract of the plant showed cognitive enhancing and antioxidant properties in Streptozotocin induced cognitive impairment and oxidative stress in rats (27). Aqueous extract decreased the Pentylenetetrazole-kindled seizures and showed improvement in the learning deficit induced by PTZ kindling suggesting its potential to anti epileptic drugs with an added advantage of preventing cognitive impairment (28). Treatment during postnatal developmental stage with the aqueous extract influenced the neuronal morphology and promoted the higher brain function of juvenile and young adult mice (29).

Neuroprotective

Asiatic acid exerted significant neuroprotective effects on cultured cortical cells by potentiating of the cellular oxidative defense mechanism. Therefore, it may prove efficacious in protecting neurons from the oxidative damage caused by exposure to excess glutamate (30).

Antidepressant

The total triterpenes present in plant had antidepressant activity in forced swimming mice and ameliorated the imbalance of amino acid levels (31). Triterpenes showed antidepressant effect and caused significant reduction of the corticosterone level in serum and increase in the contents of monoamine neurotransmitters in rat brain (32).

Tranquilizing and Sedative

Centella saponins exhibited sedative action in rats and mice. It has weak sedative but cardiodepressant and hypotensive action. The alcoholic extract produced a tranquilizing

effect in rats (33) and the glycosidal fraction showed a sedative effect. Brahmoside possessed sedative action in rats equivalent to that of a minor tranquilizer. Experimental studies on the psychotropic effects in rats showed a significant barbiturate hypnosts potentiation effect, besides producing significant alterations in the neurochemistry of the brain. The histamine and catecholamine contents in the brains of the treated group increased significantly (34). Alcoholic extract of the herb prolonged the hypnotic effect of sodium phenobarbitone in rats and decreased the acetylcholine and histamine content of the whole brain while catecholamine was increased. Its effect on the central nervous system resembled that of Chlorpromazine and Reserpine. It also had an anti-amphetamine activity and produced hypothermia, reduced the motor activity and was a potential neuroleptic (35). A depressant property was detected in this herb and Barbiturate hypnosis potentiating effect was observed in different fractions of extract (36, 37).

Anxiolytic

Centella asiatica was evaluated for its anxiolytic properties. Various paradigms were used to assess the anxiolytic activity of its hexane, ethyl acetate and methanol extracts and asiaticoside, including the elevated plus maze (EPM), open field, social interaction, locomotor activity, punished drinking (Vogel) and novel cage tests. The EPM test revealed that *Centella*, its methanol and ethyl acetate extracts as well as the pure asiaticoside, imparted anxiolytic activity (38).

Nerve regeneration

Oral administration of ethanolic extract of the plant to male Sprague-Dawley rats elicited a marked increase in neurine outgrowth in human SHSY5Y cells in the presence of nerve growth factor (NGF). Sub-fractions of the extract were tested for neurine elongation in the presence of NGF. Maximum activity was found with a non-polar fraction (GKF4) and Asiatic acid. Finding 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. Therefore *Centella* ethanolic extract may be useful for accelerating repair of damaged neurons (39).

Gastric ulcer healing

Asiaticoside isolated from the extract of the plant prevented development of gastric ulceration induced by cold in Charles-Foster rats. Ethanolic extract of plant at oral dose of 100 mg/kg daily, showed marked protective action against stress induced ulceration due to the adaptogenic property of the mixture. Water extract and asiaticoside showed healing effects on acetic acid induced gastric ulcers in rats (18, 40, 41, 42).

Cardioprotective

The plant showed cardioprotective effect on antioxidant tissue defense system during Adriamycin induced cardiac damage in rats (43). The alcoholic extract of the whole plant showed strong cardioprotective activity in limiting ischemia-reperfusion induced myocardial infarction in rats (44).

Hepatoprotective

Centella possesses in vitro anti-hepatoma activity (45). Total glucosides of the plant have significant preventive and therapeutic effect on dimethylnitrosamine induced liver fibrosis in rats (46).

Its extract provides hepatoprotective action against CCl_4-induced liver injury in rats. This was evidenced from the present study by the inhibition of decrease in serum albumin and protein level and elevation in the serum marker enzymes - AST, ALT and ALP. Administration of the extract effectively inhibited fatty changes and round cell infiltrate in hepatocytes in a dose-dependent manner. The results of the present study are comparable with studies conducted with silymarin and curcumin. Previous studies showed that administration of asiaticoside, an isolated constituent of *Centella asiatica* Linn., significantly increased the levels of antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase in excision-type cutaneous wounds in rats. Antioxidants such as ellagic acid and curcumin had been reported to protect liver injury and fibrosis induced by hepatotoxins. Hence the hepatoprotective effects of the plant in the present study might be due to the potent antioxidant action of asiaticoside present (14.5%) in the plant extract (47).

Topical

Wound healing

Extract of this plant containing madecassic acid, asiatic acid and asiaticoside accelerates cicatrisation and grafting of wounds. Total triterpenoid fraction extracted from herb increased the percentage of collagen in cell layer fibronectin and thus may help in promoting wound healing (48). Madecassic acid, asiatic acid and asiaticoside isolated from the plant are effective locally on wounds in rats. Asiaticoside facilitates wound healing through an increase in peptidic hydroxyproline content, tensile strength, collagen synthesis, angiogenesis and epitheliazation, as shown in animal models (49, 50). Oral and topical administration of an alcoholic extract increased cellular proliferation and collagen synthesis at the wound site, as evidenced by increase in DNA, protein and collagen content of granulation tissues on rat dermal wounds. The extract treated wounds were found to epithelialize faster and the rate of wound contraction was higher, as compared to control animals (51).

Anti ageing

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 has shown to induce Type I collagen synthesis in human dermal fibroblast cells by phosphorylation of both Smad 2 and Smad 3. Asiaticoside-induced binding of Smad 3 and Smad 4 was detected. Findings resulted in the nuclear translocation of the Smad 3 and Smad 4 complex pointing to the involvement of asiaticoside in Smad signaling. In addition, SB431542, an inhibitor of the TGF beta 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, the Lee,s study show that asiaticoside can induce type I collagen synthesis via the activation of the TbetaRI kinase-independent Smad pathway (52).

Cytotoxic and anti-tumour

Oral administration of the crude extract of the plant and its partially purified fractions retarded the development of tumours and increased the life span of these tumour bearing mice. Cytotoxic and anti-tumour effects involve direct action on DNA synthesis (53). A partially purified fraction of methanol extract of the herb inhibited the growth of tumour cells with no toxic effect against lymphocytes (54). Water extract has a chemopreventive effect on colon tumorigenesis (55). It might be useful in cancer chemotherapy as it induces apoptosis and enhances antitumour activity of vincristine in cancer cells (56). Asiatic acid was found to have effect on skin cancer (57).

Antioxidant

Crude methanol extract of *Centella* showed antioxidant activity on lymphoma-bearing mice (58). Antioxidant activity of the plant is comparable to the activities of rosemary and sage and has very good potential to be explored as source of natural antioxidants (59). As a potent antioxidant it exerted significant neuroprotective effect and proved efficacious in protecting rat brain against age related oxidative damage (60). Simultaneous supplementation of the drug significantly protects against arsenic induced oxidative stress but does not influence the arsenic concentration in liver, kidney and brain. It can thus be suggested that co-administration of *Centella* protects animals from arsenic induced oxidative stress but exhibits no chelating property (61).

lmmunomodulating

Triterpenoid saponins of *Centella* showed immunomodulatory effect (62). Oral administration of Brahma Rasayana, containing *Centella*, significantly increased white blood cell count, bone marrow cellularity, natural killer cells and antibody dependant cellular activity in mice exposed to gamma radiations. It reduced radiation induced peroxidation in the liver (63). Pectin isolated from the plant showed immunostimulating activities (64) and methanol extracts showed preliminary immunomodulatory activities (65). *Centella asiatica* Linn. and *Rhinacanthus nasutus* Linn. Kurz revealed immunomodulating activity with regard to both non-specific cellular and humoral immune responses suggesting that they may have chemopreventive or anticancer potential (66).

Crude water extracts of combinations of each of *Centella asiatica* Linn., *Maclura cochinchinensis* Lour. and *Mangifera indica* Linn. showed anti-herpes simplex virus activities (67).

Madecassoside and madecassic acid, both showed anti-inflammatory activity. Extract of *Centella* exerted antiinflammatory effects by reduction of acute radiation reaction in rats (68). A polyherbal Ayurvedic preparation Brahmi Rasayana, containing *Centella* as well as other herbs showed anti-inflammatory activity (69). The water extract and its active constituent, asiaticoside have an anti-inflammatory property that is brought about by inhibition of NO synthesis and thus facilitate ulcer healing (70).

Centella asiatica Linn. extract was tested for its radioprotective properties. Animals irradiated with ^{60}Co gamma radiation externally and treated with drug extract (100 mg/kg) exhibited significant increase in survival time. 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 (71).

Anti-Diabetic

Ayurveda, the science of life, originated for more than 5000 years in India. The plant has been traditionally used as a system of medicine to promote health and well-being, and relieve ailments using a holistic approach (72). In this country, a proportion of the population follows this system of medicine, either solely or in combination with allopathic medicine. Diabetes management in Ayurveda includes diet, behaviour and herbal modalities. Various herbs have been described with anti-hyperglycemic actions. Some of these like karela, turmeric, spinach, fenugreek seeds among others, can be part of a healthy die (73).

The use of herbal medicines for the treatment of Diabetes mellitus has gained importance throughout the world. The World Health Organization also recommended and encouraged this practice especially in countries where access to the conventional treatment of diabetes is not adequate (74). There is an increased demand to use natural Products with antidiabetic activity due to the side effects associated with the use of insulin and oral hypoglycemic agents. The available literature shows that there are more than 400 plant species showing hypoglycemic activity (75). Though some of these plants have great reputation in the indigenous system of medicine for their antidiabetic activities, many remain to be scientifically established. Hypercholesterolemia and hyper- triglyceridemia are common complications of Diabetes mellitus in addition to hyperglycemi (76). The frequency of hyperlipidemia in diabetes is indeed very high, depending on the type of diabetes and its degree of control. Many Indian medicinal plants are reported to be useful in diabetes. World ethnobotanical information on medicinal plants reports almost 800 plants used in the treatment of Diabetes mellitus. However, only a small number of them have been studied thoroughly (77). The cellular response to insulin is mediated through the insulin receptor (IR), which is a tetrameric protein consisting of two identical extra cellular Alfa-subunits that bind insulin as well as two identical transmembrane Beta-subunits that have intracellular tyrosine kinase activity (78). Insulin resistance, an important feature of Type 2 diabetes, is manifested as attenuated insulin receptor (IR) signaling in response to insulin binding. A drug that promotes the initiation of IR signaling by enhancing IR autophosphorylation should, therefore, be useful for treating type 2 diabetes.

As early as in 1950s, found that *Centella asiatica* Linn. (79) might have benefits on refractory wounds, such as leprosy, lupus and ulcers. While, other scientists studied the composition of *Centella* and its key ingredient is Asiatic acid, which is a pentacyclic triterpene (80). The plant contains fatty acids, sterols and alkaloids (81).Very few studies are available, to show the relationship between *Centella asiatica* Linn. and diabetes.

In the present article, an attempt has been made to study the Biochemical, Phytochemical and other Pharmacological effect of its leaves and probable link between effects of *Centella asiatica* Linn. in Diabetes mellitus has been reviewed.
It is possible that the drug may be acting by potentiating the pancreatic secretion or increasing the glucose uptake. Hypercholesterolemia, hypertriglyceridemia, hyperurea have been reported to occur in alloxan diabetic rat (82, 83). According to Dave et al., 2004, the two glycosides, brahmoside and brahminoside, which are principle constituents of *Centella asiatica* Linn. have been shown to exert sedative and hypoglycemic effects in experimental rats (84). This is in support of the finding which shows that its extracts are effective against alloxan induced diabetic rats. Repeated administration of the extracts has decreased the blood glucose, urea, total cholesterol and triglycerides significantly (85). Wide spread attention has been focused to isolate the active constituents from its butanolic extract and on the involvement of oxygen free radicals in pathogenesis of Diabetes Mellitus (86). Cellular enzymatic (SOD) and non-enzymatic antioxidants (GSH) act as primary line of defense to cope with the deleterious effects of these radical species (87).

Since redox imbalance has been incriminated in Diabetes mellitus, it is natural to expect that antioxidant defense system may be involved to counter-balance the pro-oxidant environment (88). Indeed, there is a body of evidence suggesting that antioxidant components become weak probably due to extra utilization and these antioxidants have therapeutic value (89).

Histopathological study on rat liver was undertaken for 5 days by Kanter which showed significant results. In the diabetic group, degeneration and necrosis of the islets were observed in the pancreas (90).

The cytoplasm of peri-acinar hepatocytes showed either a single large or multiple small round empty vacuoles that distended the cell cytoplasm and displaced the nucleus to the periphery in histological sections of liver stained with haematoxylin and eosin. These degenerative changes were also seen, to a lesser extent, in the midzonal regions. Parenchymatous degeneration was observed in the peripheral regions. Dissociation of hepatocytes and sinusoidal dilatation occurred due to these changes**.** The degenerated cortex and medulla and necrosis of tubules were observed in nephron of diabetic groups. The glomerulus was emptied and distal tubules also damaged in the diabetic nephron. These histopathological changes were restored by treatment with the extracts of *Centella asiatica* Linn.

The liver of control rats appeared to be divided into the classical hepatic lobules; each is formed of cords of hepatocytes radiating from the central vein to the periphery of the lobule. The cell cords were separated by narrow blood sinusoids. The histopathological examination of diabetic rats showed periportal necrosis of the hepatocytes near the portal areas. The livers also showed dilated and congested portal vessels as well as areas of inflammatory cell infiltration**.** In diabetic rats treated with *Centella asiatica* Linn., the liver architecture appeared more or less like control with the exception of some hemorrhagic areas in the blood sinusoid (47).

The cellular integrity and architecture of pancreas were intact in the normal group. Pancreatic sections stained with hematoxylin and eosin showed that alloxan caused severe necrotic changes of pancreatic islets, especially in the centre of islets. Nuclear changes, karyolysis, disappearance of nucleus and in some places, residue of destroyed cells were visible. Relative reduction of size and number of islets especially around the central vessel and severe reduction of *β*-cells were clearly seen (91).

In the study, the pancreatic *β*-cells were destroyed with the help of alloxan. Alloxan is one of the usual substances used for the induction of diabetes mellitus apart from streptozotocin. Alloxan has a destructive effect on the beta cells of the pancreas (92). The pancreas is the primary organ involved in sensing the organism's dietary and energetic states *via* glucose concentration in the blood. In response to elevated blood glucose, insulin is secreted.

Histopathological study of diabetic untreated rats showed degeneration of pancreatic islet cells, which was due to alloxan used in this study. This probably gave rise to insulin deficiency. Insulin deficiency (or diabetes mellitus) causes excessive elevation of blood glucose and underutilization leading to hyperglycemia (93). The histopathological study of diabetic treated group indicated increased volume density of islets and increased percentage of *β*-cells, in the diabetic rats that received the extracts, which may be a sign of regeneration. Signs of regeneration of *β*-cells, potentiation of insulin secretion from surviving *β*-cells of the islets of Langerhans and decrease of blood glucose have been reported following consumption of some plant extracts (94). The extract may have some chemical components that exert regenerative effects on *β*-cells, stimulate these cells to produce more insulin (pancreatotrophic action) or may have some insulin like substances. Induction of regenerative stimulus in diabetic state triggers pancreatic regenerative processes, hereby restoring functional activities of the pancreas (95). A higher dose of the extract has a greater restorative

effect on the islet cells of diabetic rats than a lower dose of extract. The hypoglycemic effect was more pronounced in alloxan-diabetic rats than in normal rats (96).

The findings of this reference indicate that consumption of the extract of *Centella asiatica* Linn. exerts significant hypoglycemic effect in diabetic rats. Histopathological studies of the pancreas and liver of diabetic treated rat show evidence of signs of regeneration of *β*-cells in groups receiving extracts. These findings support the traditional use of *Centella* leaves for controlling hyperglycemia in diabetics, in view of the restorative (protective) effects of the extract on pancreatic islet cells. The findings may indicate the presence of some hypoglycemic agents in *Centella asiatica* Linn. which have been concentrated in the extracts. The hypoglycemic effects of plants may be due to the presence of insulin-like substance in plants (97), stimulation of *β*-cells to produce more insulin, increasing glucose metabolism (98) or regenerative effect of plants on pancreatic tissue (99).

However, treatments of the diabetic rats with the extracts of *Centella* (250 mg/kg/day) showed a significant decrease in blood glucose and increases in insulin level and improved lipid profile as cholesterol, TG, LDL and HDL. There are several studies which reported that, onion intake was found to improve the diabetic status, including protection of DNA against oxidative damage, hypoglycemic and hypocholesterolemic effects (100).

Anderson *et al* revealed that the polyphenolic polymers found in herbal extracts function as antioxidants, potentate insulin action and may be beneficial in the control of glucose intolerance and diabetes (101).

Streptozotocin diabetic rats exerted a significant elevation of lipid peroxides. The production of lipid peroxides was significantly decreased by administration of its extracts. This result may be due to the active compounds of *Centella asiatica* Linn. such as daily disulphides and their oxidized thiols which has been reported to have an anti oxidative effect (102). Azuma *et al* indicated that these compounds may contribute to the protective effects of *Centella asiatica* Linn. (103).

Phytoconstituents and their pharmacological activities

There are many phytoconstituents present in the plant like ascorbic acid, asiatic acid, brahminoside *etc.*Ascorbic acid acts as acidulant, antiaging, antidote *etc.* Asiatic acid is collagenic. All the phytoconstituents present in the plant with their pharmacological activities are described in **Table 2.**

Clinical pharmacology of *Centella asiatica* Linn.

In clinical trials, an extract of *Centella* in a 1% salve or 2% powder accelerated healing of wounds (104). A formulation containing Asiaticoside as the main ingredient healed 64% of soiled wounds and chronic or recurrent atony that was resistant to usual treatment (105). In an open clinical study, treatment of 20 patients with soiled wounds and chronic or recurrent atony with a galenical formulation containing 89.5% *Centella asiatica* Linn. healed 64% and produced improvement in another 16% of the lesions studied (106). Local application of an extract of the drug to second and third-degree burns expedited healing, prevented the shrinking and swelling caused by infection, and further inhibited hypertrophic scar formation (1).

Twenty-two patients with chronic infected skin ulcers were treated with a cream containing 1% extract of *Centella.* After 3 weeks of treatment, 17 of the patients were completely healed and the ulcer size in the remaining 5 patients was decreased (107). A standardized extract of *Centella* was reported to treat ulcus cruris (indolent leg ulcers) effectively in clinical trials (108). In a double-blind study, no significant effect on healing was observed in patients with ulcus cruris after oral treatment with asiaticoside (109).

Oral administration of the plant or asiaticoside and potassium chloride capsules was reported to be as effective as dapsone therapy in patients with leprosy (110). In a controlled study of 90 patients with perforated leg lesions owing to leprosy, application of a salve of the plant produced significantly better results than a placebo (111).

Clinical trials of the drug have demonstrated its antiulcer activity after oral administration (112). Fifteen patients with peptic or duodenal ulcer were treated with a titrated extract of *Centella* (60.0 mg/person). Approximately 93% of the patients exhibited a definite improvement in subjective symptoms and 73% of the ulcers were healed as measured by endoscopic and radiological observations (113).

A clinical study on *Centella asiatica* Linn. for the treatment of various venous disorders has demonstrated a positive therapeutic effect. In patients suffering from venous insufficiency that were treated with a titrated extract of the drug, venous distension and oedema improved significantly, as compared with controls (114).

Conclusion

This review describes the morphology, microscopy, traditional and folklore uses, phyto-constituents, pharmacological reports, clinical pharmacology of *Centella asiatica* Linn. The pharmacological activities performed on the plant have been focused. The plant has been used for curing various ailments, hence acts as antiulcer, gastro protective, hepatoprotective, cardio protective, antidiabetic *etc.,* the most important being neuroprotective property.

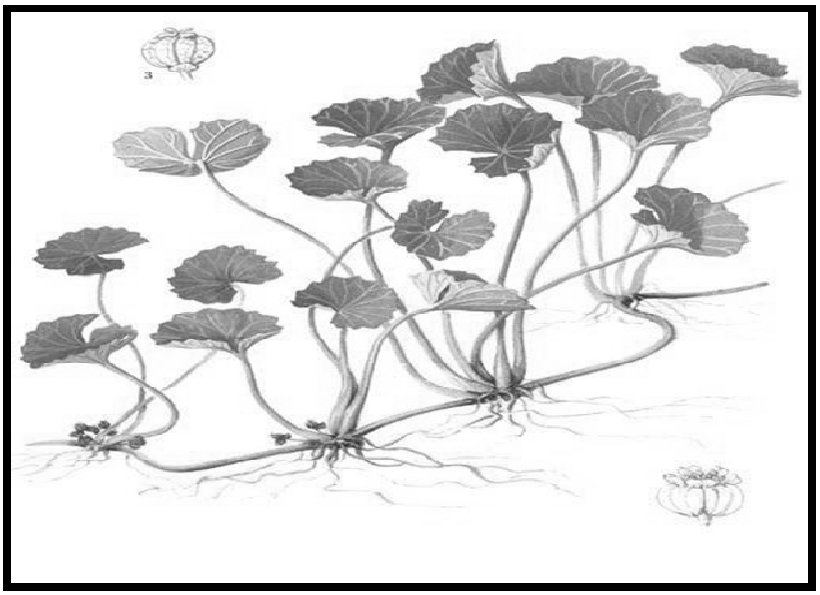

Fig 1. *Centella asiatica* Linn. plant

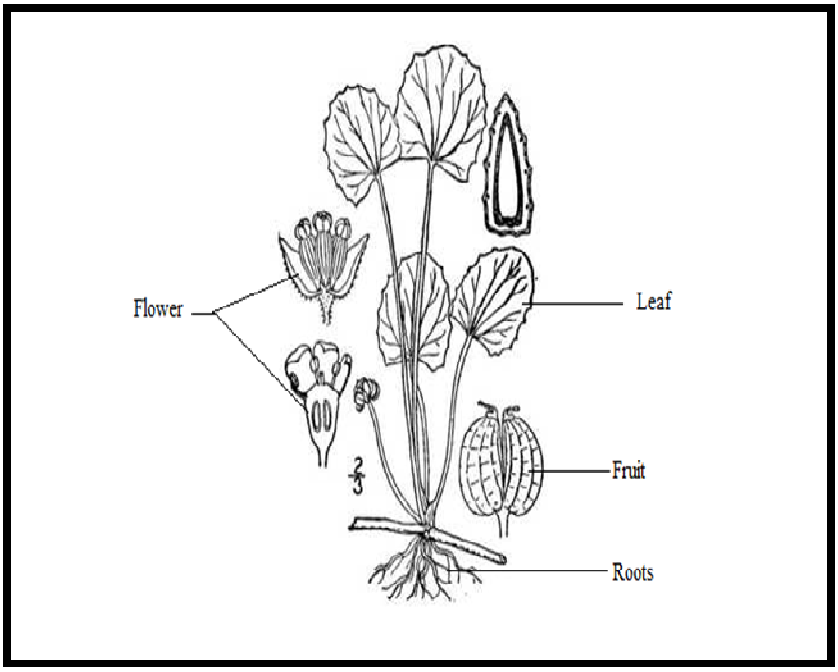

Fig. 2 Morphological description of the plant

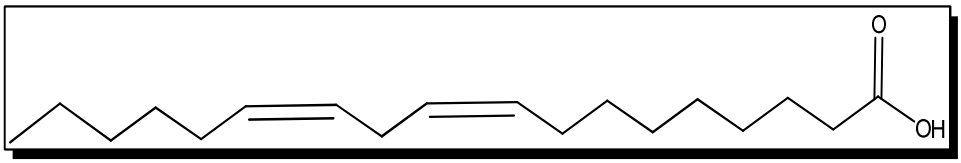

Fig. 3 Stearic Acid

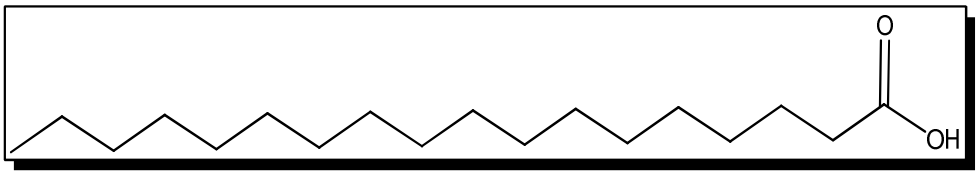

Fig. 4 Linoleic Acid

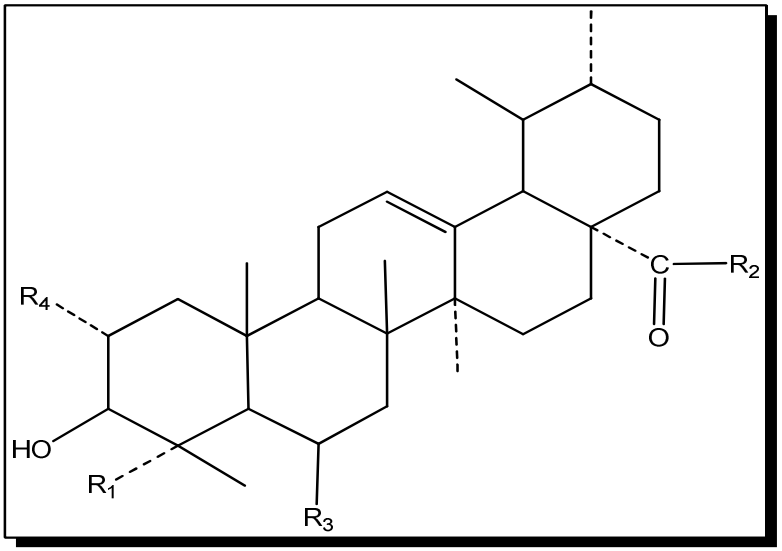

Fig. 5 Asiatic Acid Derivative

Asiatic Acid (R_1-CH_20H, R_2-H, R_3- CH_3, R_4- H),
Madasiatic Acid (R_1-CH_3, R_2-OH, R_3- CH_3, R_4- H),
Terminolic Acid (R_1-CH_20H, R_2-OH, R_3- H, R_4- CH_3),
Brahmic Acid (R_1-CH_20H, R_2-OH, R_3- CH_3, R_4- H)

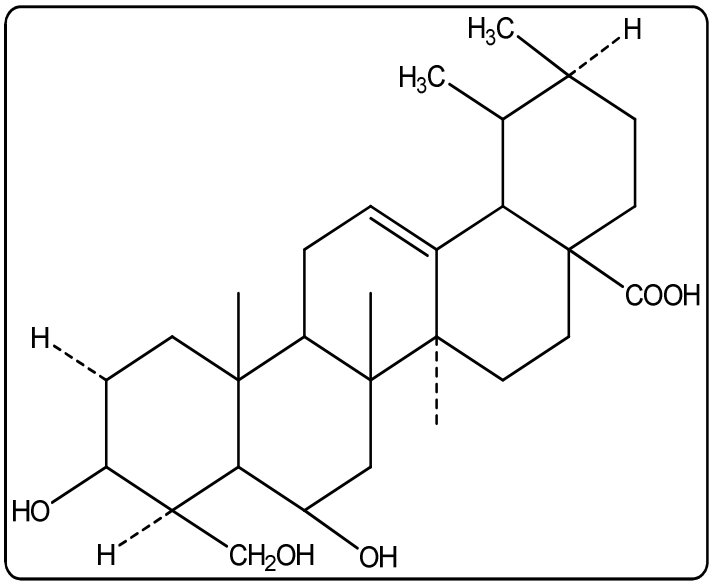

Fig.6 Isothankunic Acid

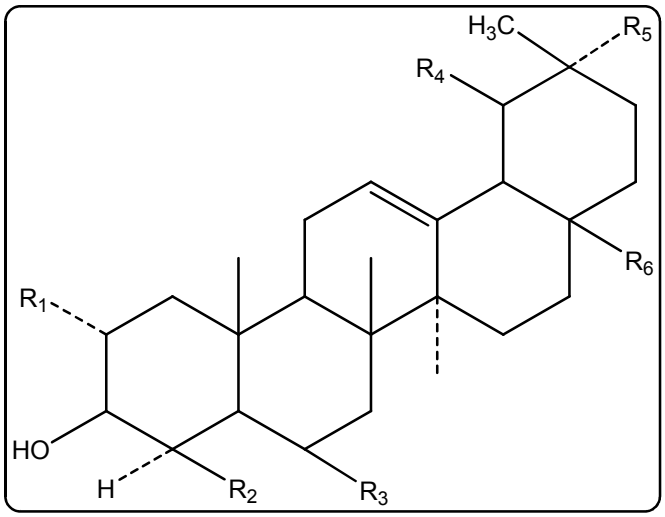

Fig.7 Asiaticoside

Asiaticoside A (R_1-OH, R_2-CH_2OH, R_3-H, R_4-CH_3, R_5-H, R_6-COO-glc(1-6)glc(1-4)rha),
Asiaticoside B (R_1-OH, R_2-CH_2OH, R_3-OH, R_4-H, R_5-CH_3, R_6-COO-glc(1-6)glc(1-4)rha),
Asiaticoside C (R_1-OH, R_2-CH_2OAc, R_3-H, R_4-CH_3, R_5-H, R_6-COO-glc(1-6)glc(1-4)rha),
Asiaticoside D (R_1-OH, R_2-CH_3, R_3-H, R_4-CH_3, R_5-H, R_6-COO-glc(1-6)glc(1-4)rha),
Asiaticoside E (R_1-OH, R_2-CH_2OH, R_3-H, R_4-CH_3, R_5-H, R_6-COO-glc(1-6)glc,
Asiaticoside F (R_1-H, R_2-CH_2OH, R_3-H, R_4-CH_3, R_5-H, R_6-COO-glc(1-6)glc(1-4)rha)

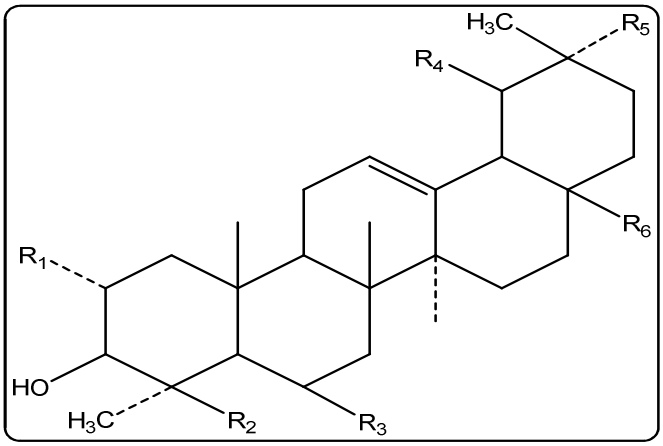

Fig.8 Centella Saponins

Centella Saponin A (R_1-OH, R_2-CH_2OH, R_3-H, R_4-H, R_5-CH_3, R_6-COO-glc(1-6)glc(1-4)rha), Centella Saponin B (R_1-OH, R_2-CH_2OH, R_3-OH, R_4-CH_3, R_5-H, R_6-COO-glc(1-6)glc), Centella Saponin C (R_1-OH, R_2-CH_3, R_3-OH, R_4-CH_3, R_5-H, R_6-COO-glc(1-6)glc(1-4)rha), Centella Saponin D (R_1-CH_3, R_2-CH_2OH, R_3-OH, R_4-H, R_5-CH_3, R_6-COO-glc(1-6)glc(1-4)rha)

Table 1. Constituent elements

Macronutrients		
Element	**Form of uptake**	**Notes**
Nitrogen	NO_3^- NH_4^+	Nucleic acids, proteins, hormones, etc.
Oxygen	O_2, H_2O	Various organic compounds
Carbon	CO_2	Various organic compounds
Hydrogen	H_2O	Various organic compounds
Potassium	K^+	Cofactor in protein synthesis, water balance, etc.
Calcium	Ca^{2+}	Membrane synthesis and stabilization
Magnesium	Mg^{2+}	Element essential for chlorophyll
Phosphorus	$H_2PO_4^-$	Nucleic acids, phospholipids, ATP
Sulfur	SO_4^{2-}	Constituent of proteins and coenzymes
Micronutrients		
Element	**Form of uptake**	**Notes**
Chlorine	Cl^-	--
Boric Acid	H_3BO_3	--
Manganese	Mn^{2+}	Activity of some enzymes
Zinc	Zn^{2+}	Involved in the synthesis of enzymes and chlorophyll
Copper	Cu^+	Enzymes for lignin synthesis
Molybdenum	MoO_4^{2-}	Nitrogen fixation, reduction of nitrates
Nickel	Ni^{2+}	Enzymatic cofactor in the metabolism of nitrogen compounds

Table 2. Phytoconstituents and their pharmacological activities

Phytonutrient	Activities
Ascorbic-Acid	Acidulant, Aldose-Reductase-Inhibitor, Angiotensin-Receptor-Blocker, AntiAGE, AntiCrohn's, Antiaging, Antiatherosclerotic, Antidecubitic, Antidepressant, Antidote (Aluminum), Antidote (Paraquat), Antiedemic, Antigingivitic, Antihepatotoxic, Antihistaminic, Antihypertensive, Antiinflammatory, Antimeasles, Antimigraine, Antimutagenic, Antiobesity, Antiorchitic, Antioxidant, Antiparkinsonian, Antiseptic, Apoptotic, Beta-Adrenergic Receptor Blocker, Beta-Glucuronidase-Inhibitor, Collagenic, Fistula-Preventive, Hypotensive, Immunostimulant, Mucolytic, Urinary-Acidulant, Vulnerary
Asiatic-Acid	Collagenic
Asiaticoside	Antiedemic, Anti-inflammatory, Antituberculic, Pilogenic, Protisticide, Vulnerary
Beta-Carotene	AntiPMS, Antiacne, Antiaging, Antihyperkeratotic, Antilupus, Antimastitic, Antimutagenic, Antioxidant, Antiphotophobic, Antiporphyric, Antiproliferant, Antistress, Antitumor, Antixerophthalmic, COX-1-Inhibitor, Colorant, Immunostimulant, Interferon-Synergist, Phagocytotic, Prooxidant, Thymoprotective
Brahminoside	CNS-Depressant, Hypertensive, Sedative, Tranquilizer, Uterorelaxant
Brahmoside	CNS-Depressant, Hypertensive, Sedative, Tranquilizer, Uterorelaxant
Gamma-Terpinene	ACE-Inhibitor, Acaricide, Aldose-Reductase-Inhibitor, Antifeedant, Antioxidant, Insectifuge
Glucose	Antiedemic, Antihepatotoxic, Antiketotic, Memory-Enhancer
Glycine	Antialdosteronic, Antigastritic, Antiprostatitic, Antipruritic, Antisickling, Neuroinhibitor
Inositol	Antidiabetic, Sweetener
Linoleic-Acid	Antiacne, Antianaphylactic, Antiarteriosclerotic, Antihistaminic, Antiinflammatory, Antiprostatitic, Comedolytic, Hepatoprotective, Insectifuge, Nematicide
Madecassoside	Antiedemic, Antiinflammatory
Niacin	AntiMeniere's, Antiacrodynic, Antiallergic, Antiamblyopic, Antianginal, Antichilblain, Anticonvulsant, Antihistaminic, Antiinsomnic, Antineuralgic, Antiparkinsonian, Antipellagric, Antiscotomic, Hepatoprotective, Sedative, Serotoninergic
Pectin	Antimutagenic, Antiobesity, Chemopreventive, Demulcent, Hemostat, Peristaltic
Riboflavin	Antidecubitic, Antikeratitic, Antimigraine, Antipellagric, Antiphotophobic
Saponins	Antihepatomic, Antimutagenic
Stearic-Acid	Cosmetic
Stigmasterol	Antihepatotoxic, Antiinflammatory, Antiophidic, Antioxidant, Artemicide, Estrogenic, Sedative
Tannin	Anthelmintic, AntiHIV, Antihepatotoxic, Antihypertensive, Antilipolytic, Antimutagenic, Antiophidic, Antioxidant, Antirenitic, Antitumor, Glucosyl-Transferase-Inhibitor, Hepatoprotective, Lipoxygenase-Inhibitor, MAO-Inhibitor, Ornithine-Decarboxylase-Inhibitor

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