Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN 2320-3862
JMPS 2017; 5(1): 78-82

Received: 11-11-2016
Accepted: 12-12-2016

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An ayurvedic herb: Enicostemma littorale blume- A review article

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Abstract
Ayurveda uses the inherent power of natural herbs to bring out wonderful results on the human body. The herbs are natural & 100% safe for human body. A perennial herb Enicostemma littorale blume (E. littorale) family Gentianaceae is cosmopolitan in occurrence in India. The bittery natured plant acts as a laxative, helps in curing fever, rheumatism, skin diseases, abdominal disorders, snake bite, obesity and helps to regulate blood sugar levels. E. littorale is rich source of alkaloids, catechins, saponins, sterols, triterpinoids, phenolic acids, flavonoids and xanthones. It also contains minerals like iron, potassium, calcium, silica, phosphate, chloride sulphate and carbonate. The plant constituents have been reported for possessing antimicrobial, antioxidant, antiulcer, antiinflammatory, hypolipidemic, hepatoprotective and hypoglycemic properties.

Keywords: Enicostemma littorale, phytoconstituents, pharmacological properties

Introduction
Plant is man's friend in survival, giving him food and fuel and medicine from the days beyond drawn of civilization [1]. Plant continue to be a major source of medicine, as they have throughout human history [2]. Enicostemma littorale Blume (Family-Gentianaceae) a glabrous herb commonly used as a bitter tonic and substitute for swertia chirayita (Roxb.ex Flem.) Karst., is also called as chhota chirayta. It is found distributed throughout the greater part of India and common in coastal areas. It is also reported to possess antitumor [3], hypoglycaemic [4] and antimalarial activities [5]. The anticancer activity of methanolic extract of the plant has been evaluated against Dalton's ascetic lymphoma in swiss albino mice [6]. Medicinal compounds derived from this plant were considered to be very effective since these were less toxic, eco- friendly, palatable, long shelf life and free from side effects [7]. *E. littorale* is a good source of iron, potassium, sodium, calcium, magnesium, silica, chloride, sulphate, phosphate and vitamins B and C [8]. In recent years, pharmaceutical companies have spent considerable time and money in developing therapeutics based upon natural products extracted from plants. The rising incidence of multidrug resistance amongst pathogenic microbes has further necessitated the need to search for newer antibiotic sources because of its abundant and widespread availability.

Detailed description of the plant

Erect perennial herb, 5–30 cm. tall, simple or branched at the base. Stem cylindric, glabrous with a decurrent ridge below each leaf. Leaves sessile (sometimes narrowed into a petiole-like base), longer than the internodes; lamina (1)5–8 x 0.3–1 cm., linear to lanceolate or narrowly oblong, entire, obtuse and mucronate at the apex, somewhat narrowing towards the base, 3-nerved from the base, glabrous. Inflorescence in many flowered axillary clusters, numerous in the axils of each pair of leaves. Flowers white with green lines, drying yellowish, sessile or subsessile; bracts long, shorter than the calyx, lanceolate-acuminate, carinate. Calyx tube 1–2 mm. long; lobes usually unequal, 0.7–1.5(2) x 0.4–0.7 mm., triangular to lanceolate, acute at the apex and narrowly scarious at the margin, or obovate to subcircular, obtuse and mucronate at the apex, with wide scarious margin. Corolla tube 3.5–6 mm. long; lobes 1.5–2 x 0.7–1 mm., ovate and abruptly narrowing to an acute or mucronate apex. Stamens inserted below the sinuses, just above the middle of the tube; filaments 1.5–2.3 mm. long, with a double hood at the insertion point; anthers. 1 mm. long, erect, shortly apiculate. Ovary 5–6 x 1 mm., ovoid; style 2–2.5 mm. long, subulate; stigma subcapitate. Capsule 3–4.5 x 2–2.5 mm., obovoid. Seeds 0.4–0.5 mm. in diam., subglobose, reticulate faveolate. (Paivera and Noguiera 1990) [9].

Taxonomy

Kingdom:	Plantae
Subdivision:	Angiospermae
Class:	Dicotyledonae
Subclass:	Gamopetalae
Serius:	Bicarpellatae
Order:	Gentianales
Family:	Gentianaceae
Genus:	Enicostemma
Species:	Littorale

Nomenclature: The word Enicostemma is probably formed from the three words, “en” means inside, “icos” means 20 and “stemma” means wreath or circle due to the many flowers arranged in circles in the leaf axils along the stem.

Vernacular names

Common names (Nadkarni 1976: 485): Ayurvedic medical: Mamejava, Mamejav, Mamejavo, Mamjjak, Mamejva; Hindi/Hindustani: Kariyatu, Chota-kirayat, Chota-chiretta, Chota-chirayata; Bombay: Kada-vinayi, Manucha; Tamil: Vallari Telugu: Nela-guli, Nela-gulimidi; Additional names: Gormadi koora (In the UK product description for Glucostat, Maharishi Ayurveda Products (2006), incorrectly refers to E. littorale as Indian Gentian; this English common name generally refers to Swertia spp. Whitehead is a common name that applies to E. verticillatum, in the New World. [10].

Phytoconstituents of *E. littorale*

This plant comprises of different chemical compounds. Many compounds have been isolated from the plant, *E. littorale*. Tanna *et al.* reported that the aerial part of the plant gave 34% of dry alcoholic extract and 15.7% of ash [11]. Natarajan and Prasad reported the presence of five alkaloids, two sterols and volatile oil. Betulin, a triterpene sapogenin was also isolated by earlier workers [12]. Monoterpene alkaloids like enicoflavin, gentiocrucine and seven different flavonoids were isolated from the alcoholic extract and the structures were identified as apigenin, genkwanin, isovitexin, swertisin, saponarin, 5-o glucosylswertisin and 5-o glucosylisoswertisin were also isolated by Goshal *et al* [13]. The presence of catechins, saponins, steroids, sapogenin, triterpenoids, flavonoids and xanthones and a new flavone C-glucoside named as Verticilliside was isolated for the first time this species was reported by Jahan *et al* [14]. Swertiamarin compound was isolated from *E. littorale* by using alcoholic extract [15]. Six phenolic acids like vanillic acid, syringic acid, p-hydroxy benzoic acid, protocatechuic acid, p-coumaric acid and ferulic acid were also found by Desai *et al* [16]. Methanol extract of *E. littorale* was found to be containing different aminoacids like L-glutamic acid, tryptophan, alanine, serine, aspartic acid, L-proline, L-tyrosine, threonine, phenyl alanine, L-histidine monohydrochloride, methionine, iso leucine, L-arginine monohydrochloride, DOPA, L-Glycine, 2-amino butyric acid and valine [17]. Swertiamarin is a representative constituent of many crude drugs, which are marketed in Japan and other countries and these crude drugs are normally evaluated by their high swertiamarin content [18, 19].

Nutritional information: According to a nutritional analysis of E. littorale by the National Institute of Nutrition, Indian Council of Medical Research, 100g fresh E. littorale greens contain 140 Kcal energy, 7g protein, 0.7g fat, 26.5g carbohydrates, 4.2g fiber, 8.4g minerals, 49.9mg iron, 1,641mg calcium, 81mg phosphorous, and 53.2g moisture (Dalit Database 2006). Based on this analysis, 100g of fresh E. littorale daily would be highly nutritious and recommended.

Pharmacological properties of *E. littorale*

1. Antimicrobial activity of E. littorale

Tanna *et al.* reported the antifungal activity of *E. littorale* blume [15]. The chloroform extract shows pronounced activity against *Aspergillus niger* (*A. niger*) and negligible activity against *Candida albicans* (*C. albicans*) at the concentration of 100, 200 µg/mL. The ethyl acetate extract shows slight activity against *A. niger* and moderate activity against *C. albicans*. The ethanol extract shows pronounced activity against *A. niger* and *C. albicans*.

Praveena *et al.* observed that the antimicrobial activity of *E. littorale* against many pathogenic microorganisms by using different solvents like chloroform, ethyl acetate, methanol, petroleum ether [20]. Among that methanolic and ethyl acetate extract of *E. littorale* showed a prominent antibacterial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi, Shigella sonnei* and antifungal activity against *Aeromonas hydrophila, C. albicans.*

2. Antihelminthic activity of E. littorale

Mishra and Shukla reported that *E. littorale* exhibits antihelminthic effects. Petroleum ether and ethanolic extracts of aerial parts of *E. littorale* Blume were prepared and evaluated separately for finding an antihelminthic effect on adult Indian earthworm, *Pheretima posthuma* [21]. Five different concentrations of each extracts were used in this antihelminthic activity, in which the time of paralysis and death of the worm were determined. The results indicated that an ethanolic extract of *E. littorale* was more potent than the petroleum ether extract.

3. Antinociceptive effect of E. littorale

Many traditional Indian medicinal plants which contain large quantity of secoiridoid, swertiamarin are being used to relieve pain. Iridoids present in a wide variety of medicinal plants

possess a large number of medicinal properties. In the study by Jaishree V, *in vivo* anti-nociceptive activity of swertiamarin isolated from *E. axillare* was carried out using three different methods in mice [22]. In the hot plate method, a significant increase in the latency period was observed for the treatment with swertiamarin at 100 and 200 mg/kg body weight after 30 and 45 min. The percent protection observed after 45 min was 109.42, 147.42 and 157.14, respectively, for the standard paracetamol and swertiamarin at 100 and 200 mg/kg body weight treatments. A significant increase in the tail withdrawal reflex was observed for the swertiamarin treatment at both the doses with percent protections of 150 and 200, respectively. In both these methods, swertiamarin showed potent activity than standard paracetamol. In the acetic acid induced writhing, swertiamarin at 100 and 200 mg/kg body weight reduced the number of writhes significantly. Dose dependent results were observed in all the three methods and among the two doses, swertiamarin at 200 mg/kg body weight showed potent activity. These results proved that swertiamarin from *E. axillare* possess both peripheral and central antinociceptive activity [22].

4. Antioxidant activity of E. littorale

Hyperlipidaemia is an important complication of alcohol induced liver injury since it accumulates cholesterol and triglycerides in the liver as well as in the blood leads to several complications [23]. Thirumalai *et al.* investigated the hyperlipidaemic condition and antioxidant effects on hepatically injured male albino rats (ethanol induced) by treating with aqueous leaf extract of *E. littorale* at a dosage of 250 mg/kg body weight. After administration of aqueous leaf extract of *E. littorale*, levels of cholesterol, triglycerides and free fatty acids were decreased in serum and the activity levels of TBARS and lipid peroxidation levels were decreased and SOD, CAT, GPx were increased in liver tissue. He reports that an aqueous leaf extract of *E. littorale* blume has potent restorative effect on hyperlipidaemic and oxidative stress.

Clinically the usages of aminoglycosidic antibiotics were limited since it induces the nephrotoxicity. Oxidative stress is the main reason for this complication. Mukundray *et al.* investigated the role of *E. littorale* Blume as a promising antioxidant therapy in gentamicin induced nephrotoxicity in rats [24]. Treatment with *E. littorale* ameliorates antioxidant defense system of mitochondrial as well as postmitochondrial fraction, with better improvement seen in mitochondrial fraction. *E. littorale* extract was used in antioxidant therapy to counteract mitochondrial and post-mitochondrial oxidative stress generated in kidney upon gentamicin treatment, thus prevented nephrotoxicity.

5. Antiulcer and anti-inflammatory activity of E. littorale

The aerial parts of *E. littorale* against aspirin, ethanol and pyloric ligation induced ulcers in rats and bovine serum albumin (BSA) denaturation were examined for antiulcer and anti-inflammatory effects by Roy *et al* [25]. The extract was administered to the overnight fasted rats, one hour prior to aspirin or alcohol or pyloric ligation challenge. The ulcer index, tissue GSH levels and lipid peroxidation levels in all the models of ulcers and the volume of gastric secretion, acidity and pH were estimated in the pyloric ligation model of ulcers. Pre-treatment with the aqueous extract of *E. littorale* showed a dose-dependent decrease in the ulcer index against aspirin, ethanol challenge and pyloric ligation. The prior administration of the aqueous extract also reduces the total acidity, free acidity, volume of gastric secretion and elevated the gastric pH. In addition, it was also observed that the aqueous extract inhibits the serum albumin denaturation in a dose-dependent manner. It was reported that the methanolic extract of *E. littorale* possesses antiulcer activity. And its anti-inflammatory activity may be attributed to the antioxidant potential.

6. Antitumour activity of E. littorale

The antitumour activity of methanolic extract of *E. littorale* has been evaluated against Dalton's ascitic lymphoma (DAL) in Swiss albino mice by Kavimani *et al*. A significant enhancement of mean survival time of methanolic extract of *E. littorale* treated tumour bearing mice was found with respect to control group. Treating with methanolic extract of *E. littorale* enhances peritoneal cell counts. When these methanolic extract of *E. littorale* treated animals underwent intraperitoneal inoculation with DAL cells, tumour cell growth was found to be inhibited. After 14 days of inoculation, methanolic extract of *E. littorale* is able to reverse the changes in the haematological parameters, protein and PCV consequent to tumour inoculation [6].

7. Hepatoprotective activity of E. littorale

Paracetamol induced hepatic injury is commonly used as an experimental model for the study of hepatoprotective effects of medicinal plant extracts and drugs. Highly reactive trichloro free radical formation, which attacks polyunsaturated fatty acids of the endoplasmic reticulum, is responsible for the hepatotoxicity of paracetamol. It produces hepatotoxicity by altering liver microsomal membranes in experimental animals. The study by Gite *et al.* [26]. revealed that the extract was able to reduce all the elevated biochemical parameters since it has hepatotoxin detoxication property. *E. littorale* possesses a chemical compound called swertiamarin which has antioxidant and hepatoprotective properties against D-GalN induced hepatotoxicity given at 100 and 200 mg/kg body weight orally for 8 days, which might be due to its *in vitro* antioxidant activity [27]. The present investigation indicates that the ethanolic extract of *E. littorale* exhibits significant hepatomodulation against oxidative stress induced liver injury by CCl_4 in rats through antioxidant potential and free radical scavenging activities along with reduction of fat metabolism [28]. These attributes provide the rationale for the use of *E. littorale* in liver disorders by traditional healers in India [29].

The hepatomodulatory response of ethanol extract of *E. littorale* Blume were examined for oxidative stress induced liver injury by carbon tetrachloride (CCl_4) in albino wistar male rats. The hepatic marker levels aspartate transaminase and alanine transaminase, alkaline phosphatase, acid phosphatase, gamma glutamyl transpeptidase, lactate dehydrogenase, sorbitol dehydrogenase, total bilirubin, total protein and albumin in serum were also restored to normal level dose-dependently after the supplementation of *E. littorale* extract in comparison to respective controls. Gupta *et al.* suggested that hepatomodulation by *E. littorale* Blume against oxidative stress mediated through interference with free radical generation and reduction in fat metabolism [28].

8. Antihyperlipidaemic activity of E. littorale

The aerial part of the *E. littorale* reduces the serum cholesterol level in hepatoma bearing rats which induces hypercholesterolaemia. A component of plant enhances cholesterol acyltransferase by esterification of free cholesterol

in the HDL [30]. A new study demonstrates a new property of swertiamarin as a potent lipid lowering agent when compared to atorvastatin and it may also contributes cardioprotective and antiatherosclerotic role effects. The swertiamarin and atorvastatin when orally fed also lowered the total serum cholesterol and triglycerides [31]. Hypolipidemic and antioxidant effects were evaluated by administrating an aqueous extract of *E. littorale* to rats (1.5 g/100 g body weight/day) along with hypercholesterolaemic diet for 6 weeks. The treatment with this extract decreases the activities of erythrocyte CAT, SOD and LPO levels, with an increase in reduced glutathione levels, liver and kidney cholesterol levels were also decreased in *E. littorale* treated rats when compared to cholesterol fed untreated rats [32].

9. Hypoglycemic activity of E. littorale

The effect of an aqueous *E. littorale* whole plant extract on antioxidant defense in alloxan-induced diabetic rats was observed by Prince and Srinivasan [33].Treating diabetic rats with oral administration of aqueous *E. littorale* whole plant extract daily for 45 days significantly decreases the blood glucose, TBARS, SOD, CAT and GPx. The effectiveness of *E. littorale* extract was compared with standard drug insulin. It was observed that an administration of insulin (6 units/kg) to alloxan induced diabetic rats for 45 days brought back all the parameters to near normal status. *E. littorale* extract at the dose of 2 g/kg was more effective. Hence it can be tried in clinical purpose to overcome these complications.

Vishwakarma *et al.* standardized the dose dependent effect with hot and cold aqueous extracts of *E. littorale* for three weeks in STZ induced type 1 diabetic rats [34]. Treatment of diabetic rats with hot aqueous extract of *E. littorale* reduced the food, water intake and glucose and AUC glucose levels and decreased the serum glucose, serum cholesterol and triglyceride levels. TLC finger-print profiles were established for the aqueous extract using high performance thin layer chromatography. Swertiamarin was found to be a major component in hot extract of *E. littorale* while it was absent in cold extract. The result suggested that *E. littorale* possesses potential antidiabetic activity and improves lipid profile at a dose of 0.5 g/kg.

10. Antihyperinsulinemic activity of E. littorale

Insulin resistance is responsible for the development of hyperglycemia in NIIDM patients. Aqueous extracts of *Aegle marmelos* and *E. littorale* reduces hyperglycaemic conditions in diabetic animal. Insulin resistance was induced in wistar rats by fructose rich diet (60% for 15 days). Treated groups received fructose diet plus aqueous extracts *A. marmelos* (500 mg/kg/day) and *E. littorale* (2 g/kg/day). Body weight, serum glucose, insulin, C-reactive protein and triglycerides levels were estimated after treating with an extract. Gohil *et al.* reported that the fructose feeding for 15 days significantly increased the serum glucose, insulin, C-reactive protein and triglycerides levels compared to control [35]. Administration of aqueous extracts of *A. marmelos* and *E. littorale* for 15 days prevented hyperglycemia and hyperinsulinemia induced by a diet high in fructose.

11. Diabetic neuropathy activity of E. littorale

Poor glycemic control and oxidative stress is one of the main reasons for the development of diabetic neuropathy. The protective effects of *E. littorale* Blume was investigated for hypoglycemic and antioxidant effect in alloxan induced diabetic neuropathy in male Charles foster rats by Bhatt *et al* [36]. Nociceptive responses were compared by formalin and tail flick in hot immersion test in both diabetic and non diabetic rats. Treating with *E. littorale* extract for 45 days significantly improved nociception in diabetic rats. The changes in lipid peroxidation and antioxidant enzymes like SOD, GPx and CAT levels, decrease in $Na\text{-}K^+$ ATPase activity were also restored by *E. littorale* treatment. This study provides an experimental evidence for the preventive effect of *E. littorale* on nerve function and oxidative stress in animal model of diabetic neuropathy. Hence, *E. littorale* may be clinically tried for treating diabetic neuropathy since it was used as a folklore medicine in diabetic patients.

12. E. littorale as a new target for islet neogenesis

Gupta *et al.* highlighted an islet neogenic property of one herbal plant *E. littorale* Blume [37]. An active herbal compound SGL-1 was isolated and purified from extract of *E. littorale* and used to differentiate two model stem cell lines PANC-1 and NIH3T3 which showed tremendous islet neogenic potential and significant islet yield compared to control serum free medium. Morphological, molecular and immunological characterization of newly generated islet like cellular aggregates proved them differentiated and positive for islet hormones. Functional characterization of ICA's confirmed significant glucose responsive insulin release. This preliminary data does offer exciting possibility of alternate source for increasing islet mass which can be used for the treatment of diabetic patients.

Conclusion

Traditional medicine system of India comprised varieties of plants which are playing a significant role in curing diseases from ancient times. Among them, *Enicostemma littorale* blume (*E. littorale*) a stomachic, bitter tonic, carminative to reduce fever [38]. and as a tonic for appetite loss [39]. In Indian ayurvedic medicine, *E. littorale* is taken in combination with other herbs, especially for diabetes. *E. littorale* is administered in ayurvedic pill form for treating type 2 diabetes since it plays a major role in reducing blood glucose and increases serum insulin level and significantly improves kidney function, lipid profile, systolic and diastolic blood pressure and pulse rate [40]. The plant constituents have been reported for possessing antimicrobial, antioxidant, antiulcer, antiinflammatory, hypolipidemic, hepatoprotective and hypoglycemic properties. This review provides taxonomy, geographical distribution, phytoconstituents and pharmacological properties of *E. littorale*.

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