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Pharmacological and Therapeutic Insights into Enicostemma littorale Blume: a Comprehensive Review

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ABSTRACT:
The traditional medicinal system uses a variety of medications that have a long history in medicine and are derived from plants and trees. Medicinal herbs have been utilized for centuries to heal a variety of ailments. Enicostemma littorale Blume is a global species that grows in India and is a perennial herb in the Gentianaceae family.
It is a bitter natural plant used as an essential indigenous medicine to treat a range of ailments like snake bites, rheumatism, skin conditions, obesity, tooth decay, laxatives, fever, and gastrointestinal problems. It also helps control blood sugar levels.Important bioactive substances found in E. littorale include triterpenoids, flavonoids, xanthones, phenolic acids, alkaloids, saponins, catechins, and sterols.In addition, the plant has silica,Potassium, calcium, iron, phosphate, carbonate, and chloride sulphate.
This review covers the pharmacological activities of Enicostemma littorale blume, including its anti-inflammatory and antiulcer properties, antihypertrophic, antidepressant, antioxidant, analgesic, antiarthritic, hypolipidemic, antipyretic, antimalarial, antiapoptotic, and cytoprotective properties, hepatoprotective, antibacterial, anti-inflammatory, hypolipidemic, and hypoglycaemic qualities. It also covers the taxonomy, geographic distribution, morphological characteristics, and phytoconstituents.
Keywords: Enicostemma littorale, Gentianaceae, phytoconstituents, swertiamarine

I. INTRODUCTION:

For many centuries, the traditional medical systems of Siddha, Unani, and Ayurveda have utilized different parts of the medicinal plant to treat a variety of illnesses. It was calculated that 72,000 different plant species have therapeutic qualities. Of which, 3 000 plant species are recognized as having therapeutic significance in India [1].

The species (Enicostemma littorale) is essential to human health. In traditional medicine, E. littorale plant parts like leaves and roots were used as remedies for several diseases, such as diabetes, leprosy, malaria, and skin disorders. The leaves helps lower obesity and has hepatoprotective, hepatomodulatory, antioxidant, and hypoglycemic qualities[2].This plant yields pharmaceutical compounds that are regarded as very beneficial due to its low toxicity, environmental friendliness, flavor, extended shelf life, and lack of adverse effects.

Good concentrations of iron, potassium, sodium, calcium, magnesium, silica, chloride, sulfate, phosphate, and vitamins B and C are found in E. littorale[3].

The World Health Organization (WHO) estimates that almost 80% of the world's population, especially the millions of people who reside in the vast rural areas of developing nations, get their medical requirements satisfied by herbal treatments[4].

1.1 Uses of Enicostemma littorale blume:

In India, E. littorale has long been used as a carminative to lower fever, a bitter tonic for the stomach[5], and a tonic for appetite loss[6]. In Indian ayurvedic medicine, especially for diabetes, E. littorale is used in conjunction with other herbs. E. littorale significantly enhances kidney function by reducing blood glucose and increasing serum insulin levels [7].

Rats have shown that E. littorale exhibits anti-inflammatory properties and tumor inhibition[8, 9]. Additionally, the plant includes swertiamarin, a secondary compound that has been demonstrated to depress the central nervous system (CNS) in rats [10].

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Fig 1.1:Enicostemma littorale blume

1.2 Taxonomy:

Kingdom	Plantae
Subdivision	Angiospermae
Class	Dicotyledonae
Subclass	Gamapetalae
Series	Bicarpellatae
Order	Gentianales
Family	Gentianacae
Genus	Enicostemma
Species	Littorale
Botanical name	Enicostemma littorale, Blume

Table No1.1: Taxonomical classification

Vernacular names:

Common name	Chota-kirayata
Tamil name	Vellarugu, Vallari, Arukumuli, Chakkiraviraiyantan
English name	Indian gentian, White head
Sanskrit name	Krimihrita, Magajihva, Mamajaka, Nagajiuha
Ayurvedic name	Naagjhvaa, Maamajjaka, Naahi, Maja-makkabooti, Tiksh-napatraa, Mamejav, ChhotaaChirayataa
Unani name	Naai, Naahi
Hindi	Chota-kirayator, Chotachirayata
Bombay	Kada-vinayi, Manucha
Bengali	Nagajivha
Malayalam	Vallari, Vellarugu
Kannada	Enicostemma
Telugu	Nella-galli, Nela-guli, Chevvu-kurti
Gujarati	Mamejava
Marathi	Chotachirayita, kadavinayi

Table No1.2: Vernacular names

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1.3 Geographical distribution:

This genus of tropical plants is found in South America, Africa, and Asia. E. littorale may thrive in a wide range of environments, including savannas, grasslands, woods, coastlines, and areas that are wet to extremely dry. It can even withstand extremely high salinity levels.

Its range includes common coastal locations with grasses and regions up to 450 meters in elevation throughout India. Growing in healthy soil, this plant grows larger and has wider, more expansive leaves farther from the sea than it does close to it.

Flowering and Fruiting season: July to November.

Collection: From October to November

Parts Used: Most often, the entire plant—including the leaves, flowers, stem, and roots—is used for treatment.

1.4 Morphological characters of Enicostemma littorale blume:

This herb is upright and perennial, growing 5 to 30 cm tall and either simple or branching at the base. The glabrous, cylindric stem has a decurrent ridge beneath every leaf.

The lamina (5.0-8.0×0.3-1.0) cm is untwisted to lanceolate or narrowly oblong, whole, obtuse and mucronate at the apex, considerably narrowing towards the base, 3-nerved from the base, glabrous, and sessile, sometimes narrowing into a petiole-like base, longer than the internodes. In the axils of every pair of leaves is an inflorescence in a flowery auxiliary cluster. The bracts are long, smaller than the calyx, lanceolate-acuminate, carinate, and the flowers are white with green lines, drying yellowish, and sessile or subsessile. The calyx tube is 1-2 mm long, with disparate lobes that are either obovate to subcircular, obtuse and mucronate at the apex, with a wide scarious margin, or triangular to lanceolate, acute at the apex, and narrowly scarious at the margin (0.7-1.5×0.4-0.7 mm). 3.5-6.0 mm long corolla tube; 1.5-2.0×0.7-1.0 mm ovate lobes that suddenly narrow to an acute or mucronate.

The corolla tube is 3.5-6.0 mm long, with oval lobes that taper sharply to an acute or mucronate tip (1.5-2.0×0.7-1.0 mm). Stamens with filaments 1.5–2.3 mm long and a double hood at the insertion point are placed beneath the sinuses, somewhat above the centre of the tube[11,12].

1..5 Phytoconstituents of Enicostemma littorale:

The chemical composition of Enicostemma littorale is diverse. E. littorale is a plant from which several chemicals have been extracted. This plant's aerial portion yields 15.7% ash and 34% dry alcoholic extract[13]. The qualitative examination of ash was used to assess the presence of minerals such as silica, phosphate, calcium, magnesium, potassium, sodium, iron, sulphate, carbonate, and chloride. Five alkaloids, two sterols, and volatile oil were found[14].

A triterpene sapogenin called betulin was also discovered by previous researchers. Apigenin, genkwanin, isovitexin, swertisin, saponarin, 5-o glucosylswertisin, and 5-o glucosylisoswertisin were among the seven distinct flavonoids and monoterpene alkaloids such as enicoflavin and gentiocrucine that were separated from the alcoholic extract[15].

For the first time, this species was discovered to include catechins, saponins, steroids, sapogenin, triterpenoids, flavonoids, and xanthones, as well as a novel flavone C-glucoside called Verticilliside[16].

Alcoholic extract was used to separate the swertiamarin component from E. littorale[17]. Additionally, six phenolic acids were discovered, including ferulic acid, vanillic acid, syringic acid, protocatechuic acid, p-hydroxy benzoic acid, and p-coumaric acid.

Several amino acids, including L-glutamic acid, tryptophane, 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, were discovered to be present in the methanol extract of E. littorale[18].

Many crude medications that are sold in Japan and other nations contain swertiamarin as a representative constituent. These medications are typically judged by how much swertiamarin they contain[19].

II. PHARMACOLOGICAL PROPERTIES OF ENICOSTEMMAITTORALE BLUME

2.1.1 Anti-ulcer and anti-inflammatory activity:

According to some studies, the plant's aerial parts include flavonoids, xanthines, and other compounds. The flavonoids are known to possess antioxidant, anti-inflammatory, and anti-ulcer properties. Since the methanolic extract of this plant is known to contain flavonoids and other related compounds, it is tested for gastroprotective and in vitro anti-inflammatory properties using a range of experimental models of ulcers, such as pyloric ligation, ethanol, and aspirin-induced ulcers

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in albino rats. In order to prevent bovine serum albumin denaturation and ulcers in rats brought on by aspirin, ethanol, and pyloric ligation, the aerial parts of Enicostemma littorale were examined for their antiulcer and in vitro anti-inflammatory qualities.

The rats were given the extract (200 mg/kg and 400 mg/kg p.o.) one hour before the aspirin/alcohol/pyloric ligation challenge, following a full night of fasting. All ulcer models included values for the ulcer index, tissue GSH levels, and lipid peroxidation levels; the pyloric ligation ulcer model also included estimates for acidity, pH, and stomach secretion volume. Following pretreatment with the extract (against aspirin, ethanol challenge, and pyloric ligation), the ulcer index dropped in a dose-dependent manner. Furthermore, the extract's earlier administration reduced overall acidity, free acidity, and stomach output volume [20].

2.1.2 Antihypertropic potential:

The anti-hypertrophic potential of Enicostemma littorale (E. littorale) aqueous extract was evaluated biochemically against isoproterenol-induced cardiac hypertrophic rat models (male albino Wistar rats).

E. littorale aqueous extract, which is known to have several favorable properties, was given orally (100 mg/kg, 12 days, subcutaneously) to rats with heart hypertrophic induced by isoproterenol (ISO) (low ISO: 60 mg/kg, 12 days; high ISO: 100 mg/kg, 12 days). The results were contrasted to a group that received treatment with Losartan (10 mg kg, given orally over 12 days) as the reference drug.

Heart morphometric indices, ECG tracings, changes in blood biochemical markers, including serum glucose and serum heart-specific enzymes (SGOT, SGPT, and LDH), total protein, serum albumin, lipid profile, and histological examination of the heart tissue were all used to assess E. littorale's anti-hypertrophic effect.

The results basically proved that the plant extract successfully decreased the isoproterenol-induced heart hypertrophy. In order to treat cardiac hypertrophy, the glycoside swertiamarin, which is found in this plant and has been shown to have anti-fibrotic properties in the liver, can be further separated and tested for anti-hypertrophic properties[21].

2.1.3 Antidepressant Activity:

Antidepressant Activity of Enicostemma littorale Blume in Shp2 (Protein Tyrosine Phosphatase) -inhibited Animal Model of Depression.

Methyl isobutyl ketone (100 mg/kg b.w. i.p.) and sodium orthovanadate (30 mg/kg b.w., i.p.), a protein tyrosine phosphatase inhibitor, were administered to young Wistar rats in order to create animal models of depression.An oral dose of 100 mg/kg b.w. of E. littorale aqueous extract was given. Biochemical, histological, and forced swimming test (FST) characteristics were assessed in relation to fluoxetine (20 mg/kg b.w., oral) treatment. Swertiamarin, a distinct glycoside found in the Gentianaceae family, was verified via high performance thin layer chromatography. With regard to fluoxetine, FST showed low rates of immobility in the group receiving plant extract and high rates in the depressed groups.

Histopathological research revealed disordered neuronal architecture during depression, while fluoxetine and plant extract treatment resulted in a rejuvenation of neuronal patterns. This study demonstrates the antidepressant properties of E. littorale and shows that sodium orthovanadate causes depression in mice[22].

2.1.4 Analgesic and Anti-Arthritic Effect:

The traditional remedy for rheumatic discomfort, Enicostemma littorale (Blume), was chosen for scientific verification. The analgesic and anti-inflammatory properties of the 85% methanolic extract made from the entire Enicostemma littorale plant have been assessed. The Complete Freund's adjuvant-induced arthritic model is used to assess the anti-inflammatory and antioxidant properties, while the hot plate and tail immersion approach has been used to estimate the analgesic effectiveness.

According to the findings of the hot plate and tail immersion method evaluation of analgesic efficacy, the extract shows notable activity at 150 mg/kg body weight, with a dose-dependent impact. It has been discovered that Enicostemma littorale reduces the paw volume in Freund's adjuvant-induced arthritis (15.81%). Increasing antioxidant enzymes also shows significant protection. In conclusion, in the Freund's adjuvant-induced arthritic model in rats, the 85% methanolic extract of Enicostemma littorale exhibits noteworthy analgesic and anti-inflammatory properties[25].

2.1.5 Hypolipidaemic and antioxidant effect:

Assessing the hypolipidemic and antioxidant properties of Enicostemma littorale (E. littorale) Blume (Ens) aqueous leaf extract against ethanol-induced hepatic damage in albino rats is

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the goal of this study. Six male albino rats per group were selected for the investigation. At a dosage of 250 mg/kg bw, the hypolipidemic and antioxidant effects of E. littorale Blume (Ens) aqueous leaf extract were assessed. Rats given ethanol showed elevated levels of tissue thiobarbituric acid reactive substances (TBARS), lipid hydroperoxide, and serum and tissue cholesterol, triglycerides, and free fatty acids. Glutathione peroxidase (GPX), glutathione-s-transferase (GST), catalase (CAT), and superoxide dismutase (SOD) were among the liver antioxidant enzymes whose activity levels decreased. Following the administration of the E. littorale Blume extract, blood and liver tissue levels of lipid hydroperoxide, TBARS, and cholesterol, triglycerides, and free fatty acids dropped, whereas liver tissue levels of antioxidant enzymes rises[26].

2.1.6 Antipyretic and antimalarial activities:

E. littorale's crude extract (260–780 mg/kg) and fractions (aqueous and chloroform; 520 mg/kg) were tested for antipyretic, dinitrophenol, and amphetamine-induced pyrexia, as well as antiplasmodial activity against mice infected with chloroquine-sensitive Plasmodium berghei (P. berghei).Investigations were conducted into the antiplasmodial activity during both preventive and established infections. As positive controls, pyrimethamine (1.2 mg/kg) and artesunate (5 mg/kg) were employed. The crude extract's antipyretic properties against amphetamine, dinitrophenol, and yeast-induced pyrexia were also assessed.

The extract and its fractions reduced parasitaemia caused by chloroquine-sensitive P. berghei infection in mice in preventive, suppressive, and curative paradigms in a dose-dependent manner. $P<0.001$ indicates that these decreases were statistically significant. Additionally, they increased the average survival duration from 11 to 27 days in comparison to the control group ($P<0.01 – 0.001$). The activity of the extracts and fractions were similar to those of the common medications, pyrimethamine and artesunate. When dinitrophenol, amphetamine, and yeast were employed to induce pyrexia, the extract produced dose-dependent and statistically significant inhibitions ($P<0.05$-0.001).The presence of alkaloids, cardiac glycosides, tannins, saponins, terpenes, and flavonoids was shown by the phytochemical screening of the ethanolic extract of the entire Enicostemma littorale plant.

One of the main active principles in E. littorale has been identified as swertiamarin. Since Swertia chirata has less swertiamarin than E. littorale, this component has been suggested to be the cause of its antimalarial properties. Since E. littorale has been shown to possess more swertiamarin than Swertia chirata, it may be the cause of the antiplasmodial activity seen in this investigation. More specifically, monoterpenes found in E. littorale have been linked to plant antiplasmodial properties.According to the study's findings, E. littorale has strong antipyretic and antiplasmodial properties. These validate its usage in folk medicine to treat fever and malaria[27].

2.1.7 Anti-apoptotic and cytoprotective effect:

In diabetes mellitus (DM), oxidative stress causes the Islets of Langerhans to undergo apoptosis. In rural India, the herb Enicostemma littorale blume, which belongs to the Gentianaceae family, is used as an anti-diabetic. The Trypan blue dye exclusion assay was used in this work to determine the ideal protective dose and duration for the whole plant methanolic extract of Enicostemma littorale at doses of 0.25–4 mg/mL each for a preincubation period of 0.5–4 hours against 50 mM H2O2. Islet intracellular ROS was measured using DCFDA labeling, and PS/PI and FDA/PI staining were used to measure cell death. Additional procedures included the comet assay, biochemical evaluation of caspase-3 and antioxidant enzyme activities, and immunoblotting of PARP-1, caspase-3, TNF-a activation, and p-P38 MapK (stress kinase) induction.

Throughout the investigation, the optimal dosage of Enicostemma littorale MeOH extract (2 mg/mL) for two hours was utilized, which markedly reduced total intracellular ROS and cell death. Additionally, the markedly raised levels of TNF-a, p-P38 MapK (stress kinase), PARP-1 cleavage, and caspase-3 activity were returned to normal. Pretreatment with Enicostemma littorale MeOH extract can increase antioxidant enzyme activities and protect against DNA damage, according to Comet assay results and antioxidant enzymes such as catalase, superoxide dismutase, reduced glutathione, and glutathione peroxidase[28].

2.2.1 Antioxidant properties of swertiamarin:

Insulin resistance, β cell dysfunction, visceral fat, inflammation, and chronic oxidative stress are the hallmarks of type 2 diabetes mellitus (T2DM), an endocrine illness. However, type 2 diabetes is characterized by insulin resistance, which leads to chronic hyperglycemia. Long-term hyperglycemia increases glucose's auto-oxidation

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to produce free radicals. Both macrovascular and microvascular problems arise when free radicals are produced in excess of what the body's natural antioxidant defenses can scavenge. In this study, we assessed the antioxidant capacity of swertiamarin, a secoiridoid glycoside found in the blume leaves of Enicostemma littorale, in rats with type 2 diabetes that were fed a high-fat diet and given low doses of streptozotocin. Rats were given a high-fat diet and modest doses of STZ to cause experimental type 2 diabetes.

Swertiamarin (50 mg/kg b.w./rat/day) was administered orally to diabetic rats for 30 days. Oxidative stress indicators, including protein carbonyls, hydroperoxides, and lipid peroxides, were measured. Both enzymatic and non-enzymatic antioxidant levels were assessed. Rats with diabetes displayed significantly higher levels of oxidative stress indicators and lower levels of antioxidants, both enzymatic and non-enzymatic. In diabetic rats, oral administration of 50 mg/kg bw/rat/day for 30 days resulted in a decrease in oxidative stress indicators and an improvement in antioxidant status, suggesting that swertiamarin has antioxidant qualities in addition to its antidiabetic ones[23].

2.2.2 In-Vitro Antioxidant Activity:

The antioxidant capacity and total phenolic and flavonoid contents of hot aqueous and methanol extracts of the entire Enicostemma littorale Blume plant were examined. Total phenolic and flavonoid contents in the hot methanol extract were found to be higher than in the hot aqueous extract of Enicostemma littorale, and the percentage yield of the hot aqueous extractive value (36.3%) was higher than the percentage yield of the hot methanol extractive value (21.8%). Enicostemma littorale had low antioxidant activity in DPPH, ABTS, and FRAP techniques when compared to the standard trolox, according to the overall results of in-vitro antioxidant activity experiments. No iron chelating activity was detected at the maximum concentration of both of the extracts. There does not seem to be a comparison between the extractive values and the observed in-vitro antioxidant activity and the total phenolic and flavonoid contents of Enicostemma littorale, despite the fact that the components of these compounds were identified in the hot methanol and aqueous extracts[24].

2.3 Enicostemma littorale prevents tumor formation in 7,12- dimethylbenz(a)anthracene-induced hamster buccal pouch carcinogenesis:

When compared to other nations, India has the greatest yearly incidence of oral cancer, making it one of the most prevalent cancers in the world. Oral cancer is one of several malignancies whose development has been linked to altered lipid peroxidation and antioxidant status as well as a malfunction in the detoxification cascade. This study looked into the chemopreventive potential of an ethanolic extract of Enicostemma littorale leaves (ElELet) in hamster buccal pouch carcinogenesis caused by 7,12-dimethylbenz(a)anthracene (DMBA). Using 0.5% DMBA three times a week for 14 weeks caused an oral tumor to grow in the buccal pouches of male golden Syrian hamsters. With a rise in tumor volume and tumor burden, we saw 100% tumor formation in the hamsters given DMBA alone. When hamsters were given DMBA alone, they showed imbalances in their antioxidant (superoxide dismutase, catalase, glutathione peroxidase, and vitamins E and C) and detoxification (glutathione reductase, glutathione-S-transferase, glutathione, and Deoxythymidine-diaphorase (DT)-diaphorase) status as well as lipid peroxidation by-products (thiobarbituric acid reactive substances).

Precancerous and malignant lesions in the oral cavity were considerably reduced in hamsters treated with DMBA when ElELet was given orally at a dose of 250 mg/kg body weight. ElELet suppressed oral carcinogenesis by modifying the level of antioxidants and phase I and II detoxification agents. According to this study, E. littorale's antioxidant capacity may have prevented oral carcinogenesis in hamsters given DMBA. Histological investigations conducted during DMBA-induced oral carcinogenesis further support the current discovery[29].

III. CONCLUSION

In conclusion, Enicostemma littorale Blume, a plant species traditionally used in various medicinal practices, demonstrates a promising array of therapeutic properties. Its bioactive compounds, including alkaloids, flavonoids, and saponins, contribute to its potential as an anti-inflammatory, antioxidant, and antimicrobial agent. Additionally, preliminary studies highlight its beneficial effects on liver function, blood sugar regulation, and anti-cancer properties, offering promising avenues for future pharmacological development.

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Despite the positive findings, there is a need for more rigorous clinical trials and standardized formulations to fully establish its safety, efficacy, and potential side effects. Further research is also required to better understand its mechanisms of action and how it can be integrated into modern therapeutic practices.

Overall, Enicostemma littorale Blume holds significant promise in traditional medicine, but more scientific validation is necessary to determine its role in contemporary healthcare.

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