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Exploration of *Enicostemma littorale* across Multiple Scales of Investigation (Morphological, Microscopic, Phytochemical, and Biological): A Comprehensive Analysis

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Abstract

Ayurveda, an ancient and holistic system of medicine that originated in India, utilizes natural herbs derived from their native environments to promote healing and restore balance within the body. Renowned for their safety profile and minimal side effects, these plants form the cornerstone of traditional therapeutic practices. A prominent member of this natural pharmacopeia is *Enicostemma littorale* Blume (family: Gentianaceae), a cosmopolitan perennial herb widely distributed across India. This bitter plant is esteemed in traditional medicine for its remarkable versatility in treating a wide array of ailments. Its documented ethnopharmacological applications include alleviating pain, reducing fever, and managing rheumatism, skin diseases, abdominal disorders, and obesity. Furthermore, it is extensively used to regulate blood sugar levels and has even been applied as a treatment for snake bites.

The profound therapeutic potential of *E. littorale* is attributed to its complex and rich phytochemical composition. The plant biosynthesizes a diverse array of beneficial bioactive compounds, including alkaloids, saponins, catechins, sterols, phenolic acids, triterpenoids, flavonoids, and xanthones, which act synergistically to produce its wide-ranging biological effects. This review article provides a comprehensive analysis of *E. littorale*, systematically discussing its historical ethnopharmacological uses, detailed phytochemistry, and validated biological activities. It also delivers a high-level overview of the plant's geographical distribution, key physicochemical parameters, major phytoconstituents, and multifaceted pharmacological properties. Finally, the article delves into future research trends and emerging perspectives on this medicinal plant, concluding that its full potential can only be unlocked through continued, careful phytochemical research, mechanistic studies, and the maintenance of long-term conservation efforts to ensure its sustainable availability for future generations.

Keywords: *Enicostemma littorale* Blume, Gentianaceae, Phytochemistry, Alkaloids, Catechins, Triterpenoids.

1. Introduction

Medicinal plants represent a valuable source of therapeutics for a wide spectrum of diseases,[1] forming the foundation of sophisticated traditional medicine systems such as Ayurveda, Unani, and Traditional Chinese Medicine, which have given rise to numerous important contemporary drugs.[2] In contrast, allopathic medicines can be associated with severe adverse effects that pose risks to human health.[3]

Herbal medications typically contain a complex mixture of pharmacologically active compounds; in many cases, the specific components critical to the therapeutic action remain unidentified.[4] This has led researchers to focus on traditional medicinal systems to enhance healthcare outcomes.[5] The use of medicinal plants to treat various ailments has a long history, and their popularity has grown significantly over the past decade, now benefiting approximately 20% of the global population. These plants are composed of organic compounds, with their roots, stems, leaves, and seeds often being the most potent parts. Herbs are also recognized for their rich content of nutrients, minerals, and vitamins, and are primarily valued

as natural agents with a favorable safety profile and fewer side effects.[6]

The clinical application of plants described in ancient Indian Vedas for disease treatment highlights a deep historical root. Today, traditional medical systems are widely accepted and practiced worldwide. India is unique in its recognition of multiple traditional systems, including Ayurveda, Siddha, Unani, Homeopathy, and Yoga. Because medicinal plants possess drug-like properties, they have been identified as promising candidates for modern drug development.[7]

Ayurveda, one of the world's oldest extant health systems, is grounded in fundamental principles and theory-based practices. Literally translated from Sanskrit, "Ayu" means life and "Veda" means knowledge or science.[8] Originating in India over 5,000 years ago, Ayurveda is often referred to as the "Mother of All Healing".[9] It includes topical preparations for wound healing, and its advancement relies on pharmaceuticals and supportive endeavors. Encouraging participation from raw material collectors, dealers, processing industries, practitioners, and consumers is crucial. Notably, around 1,100 medicinal plants are used in these systems, with at least 60 in high demand.[10]

The Siddha system of medicine (SSM) is an ancient Indian tradition, regarded as the mother medicine of the ancient Tamils/Dravidians in South India. The term "Siddha" signifies "established truth".[11] SSM is primarily practiced in southern India for treating various diseases, including chronic conditions.[12] While it shares similarities with Ayurveda, each system has its distinct strengths and philosophical nuances. Research in Siddha aims to provide detailed descriptive information on body constitution (Udaliyal) features, categorizing individuals based on the predominance of Vali (Vatham), Azhal (Pitham), and Aiyam (Kabam) as described in its literature.[13]

The Unani System of Medicine, founded by Hippocrates and known as Graeco-Arabic medicine, views the human body as a single unit composed of seven intrinsic components (*Umoor-e-Tabiya*): Arkan (Elements), Mizaj (Temperament), Akhlaat (Humours), Arwaah (Lifeforce), Aaza (Organs), Quwa (Faculties), and Afa'al (Functions).[14,15] This system emphasizes bodily homeostasis, which depends on the balance of the four humours and temperaments. This balance is maintained by six essential factors (*Asbab-e-Sitta Zarooriya*): atmospheric air, diet, sleep and wakefulness, elimination and retention, physical activity, and psychological state. A disturbance in any factor can alter humoural balance, disrupt homeostasis, and lead to disease.[16]

Homeopathy, systematized by Dr. Hahnemann, integrates Hippocrates' concept of "like cures like" with principles of minimal dose, personalized medicine, vital force, and the dynamization of substances.[17] Yoga, a 5,000-year-old discipline, traditionally aims to liberate oneself from suffering.[18] It is a low-cost, non-invasive practice that has demonstrated efficacy as a primary or adjunctive therapy for weight reduction, management, and the prevention of obesity and metabolic syndrome, with studies reporting significant reductions in abdominal obesity and cardiometabolic risk factors.[19]

Figure 1. White-flowered *Enicostemma littorale*.

In India, an estimated 7,500 of the 17,000 species of higher plants are known to have medicinal uses.[20] *Enicostemma littorale* Blume (also referred to as *E. littorale*) is one such plant. The genus name "Enicostemma" is derived from three Greek words: *en* (inside), *eikos* (twenty), and *stemma* (wreath), possibly referring to the internal structure of the flower.[21] The plant is known to contain numerous bioactive compounds, including alkaloids, saponins, flavonoids, steroids, tannins, proteins, and reducing sugars.[22] A daily intake of 2g of fresh *E. littorale* leaves is recommended for diabetic patients. Furthermore, reports from the Indian Council of Medical Research and other analyses confirm

that *E. littorale* is a good source of energy, protein, fat, carbohydrates, and other nutritional elements.[23]

Nutritionally, 100g of *E. littorale* provides 140 Kcal energy, 7g protein, 0.7g fat, 26.5g carbohydrates, 4.2g fibre, 8.9g minerals, 49.9mg iron, 1641mg calcium, 81mg phosphorous, and 53.4g moisture [Table 1].

The plant is characterized as pungent and bitter, and is recognized for its antihelmintic properties and benefits in treating fever and vata diseases. It is rich in diverse phytoconstituents such as alkaloids, catechins, saponins, sterols, triterpenoids, phenolic acids, flavonoids, and xanthones.[24] Traditionally, it is used as a stomachic, laxative, and anti-diabetic agent. Crushed plant material is also applied to treat snake bites and is believed to possess anticancer properties.[25] Belonging to the Gentianaceae family, *Enicostemma* is native to India (from Punjab to Kanyakumari). Fundamental information about *E. littorale* is summarized in Table 2.

Table 1. Nutritional composition of *Enicostemma littorale* per 100g.

Nutrition	Amount
Energy	140 kcal
Protein	7 g
Fat	0.7 g
Carbohydrates	26.5 g
Fibre	4.2 g
Minerals	8.9 g
Iron	49.9 mg
Calcium	1641 mg
Phosphorous	81 mg
Moisture	53.4 g

Table 2. Fundamental characteristics of *Enicostemma littorale*.

Attribute	Description
Synonyms	*E. hyssopifolium* (Willd.), *E. axillare* (Lam.) Raynal
Family	Gentianaceae
Habitat	Native to India (from Punjab to Kanyakumari)
English Name	Indian Gentian
Folk Name	Chhota Chirayata
Part Used	Whole plant
Chemistry	Bitter principles (e.g., swertiamarin), alkaloids, ophelic acid, tannins.
Action	Bitter tonic, cardio-stimulant, blood purifier, anti-inflammatory, anti-rheumatic, carminative.[26,27]

2. Methods

2.1. Literature Survey Strategy

A comprehensive literature survey was conducted to compile and analyze the available scientific information on *Enicostemma littorale* Blume. Electronic databases, primarily PubMed and Google Scholar, were searched for relevant records published from inception until December 2024. The search strategy employed a combination of keywords and Boolean operators to maximize coverage: `("Enicostemma littorale" OR "Enicostemma axillare" OR Mamajjaka OR "Chhota chirayata" OR Vellarugu) AND (pharmacognosy OR phytochemistry OR chemical constituent OR pharmacology OR biological activity OR traditional use OR therapeutic)`. This approach aimed to gather literature on the pharmacognosy, phytochemistry, and biological activities of *E. littorale*.

2.2. Selection of Relevant Literature

The identified records were screened based on their titles and abstracts against pre-defined inclusion and exclusion criteria. The full text of potentially relevant articles was then obtained and analyzed rigorously. The primary inclusion criteria were: a) studies published in the English language; b) original research articles, review articles, and authoritative books focusing on the phytochemistry of *E. littorale*; c) investigations into its pharmacological and biological activities (in vitro, in vivo, or ex vivo); and d) articles detailing its traditional uses, Ayurvedic/Siddha properties, and pharmacognostic features. The main exclusion criterion was articles focusing primarily on other species within the Enicostemma genus. This process, while thorough, did not constitute a formal systematic review with a PRISMA flow diagram but was designed for a comprehensive narrative synthesis.

2.3. Data Extraction and Synthesis

Data from the selected studies were extracted and organized into thematic sections to structure this review.

The extracted information was synthesized to create a coherent overview rather than a statistical meta-analysis. The compiled data includes: 1) Pharmacognostic profile: encompassing vernacular names, taxonomic classification, geographical distribution, morphology, and microscopy; 2) Phytochemical profile: detailing the isolated chemical constituents and their analyses; and 3) Therapeutic profile: summarizing traditional (Ayurvedic and Siddha) perspectives and the scientifically validated biological activities of E. littorale extracts and compounds.

3. Results

3.1. Pharmacognostic Profile

3.1.1. Vernacular Names

The widespread traditional use of *E. littorale* across the Indian subcontinent is reflected in its numerous vernacular names, as detailed in Table 3. These names often allude to its bitter taste (comparable to *Chirayata*, *Swertia chirayita*) or its physical characteristics.

Table 3. Vernacular names of *E. littorale*.

Language	Names
Bengali	Nagajivha
Hindi	Chota chirayata
Malayalam	Vellari
Marathi	Kada-vinayi
Telugu	Nela-guli
Tamil	Vellarugu
Sanskrit	Mamajjaka
Gujarati	Mamejavo[21]

3.1.2. Taxonomic Classification

The taxonomic classification of *E. littorale* places it within the gentian family, a group known for its bitter principles, as outlined in Table 4.

Table 4. Taxonomic classification of *E. littorale*.

Rank	Classification
Kingdom	Plantae
Subdivision	Angiospermae
Class	Dicotyledonae
Subclass	Gamopetalae
Series	Bicarpellatae
Order	Gentianales
Family	Gentianaceae
Genus	*Enicostemma*[23]

3.1.3. Geographical Distribution

E. littorale is predominantly found in tropical regions of Africa and Asia. The statement that it is "only found in Central America and the Caribbean" is inaccurate and likely refers to another species; *E. littorale* is native to India.[28] Within India, its distribution is extensive, recorded in states including Gujarat, Maharashtra, Rajasthan, Madhya Pradesh, Andhra Pradesh, Karnataka, and Tamil Nadu.[29] The species thrives in a variety of habitats, from open, moist areas to drier savannas, and is well-adapted to regions with an annual rainfall of 700-800mm.[30] It is a perennial herb.

3.1.4. Morphology

E. littorale is a glabrous, perennial herb characterized by its distinct bitter taste. Its stems are cylindrical, featuring a decurrent ridge below each leaf attachment point. The leaves are nearly sessile, with a lamina that is linear to lanceolate or narrowly oblong (ranging from 1-8 cm long and 0.3-1 cm wide), featuring three nerves arising from the base and an obtuse, mucronate apex. The inflorescence consists of dense, many-flowered clusters situated in the leaf axils. The flowers are small, sessile or subsessile, and white with green striations, drying to a yellowish colour. Key floral characteristics include a calyx with unequal lobes, a corolla tube (3.5-6.0 mm long) with oval lobes, and stamens inserted in the middle of the corolla tube with filaments featuring a distinctive double-hooded structure at their point of insertion.[31]

3.1.5. Microscopy

The microscopic anatomy provides key identifying features for the authentication of *E. littorale*.

Root: The transverse section (T.S.) of the root is circular. It is characterized by a single-layered epidermis and a broad cortex, 7-10 layers thick, composed of parenchymatous cells. The vascular tissue consists of vessels surrounded by thick-walled xylem sclerenchyma. A pith is absent in the root's center [Figure 2].[32]

Stem: The T.S. of the stem is hexangular in outline, with ridges that often extend into wing-like structures. It is covered by a single-layered epidermis with a thick cuticle. The cortex is parenchymatous, 6-15 layers thick, and contains scattered chlorenchyma cells. The stele exhibits a continuous band of phloem on either side of a xylem band

that is interrupted at the poles. A prominent parenchymatous pith is present in the center [Figure 3].[32]

Leaf: The leaf has a unistratose upper and lower epidermis, both covered by a thick, striated cuticle. The midrib region has a lobed appearance, with a single layer of hypodermis on the abaxial side. The mesophyll is not explicitly differentiated; it is described as composed of dense chlorenchyma. The lamina shows 2 layers of palisade cells towards the abaxial epidermis and 3-5 layers of spongy chlorenchyma. The epidermis bears non-glandular trichomes, which are multicellular with a single basal cell [Figure 4].[33]

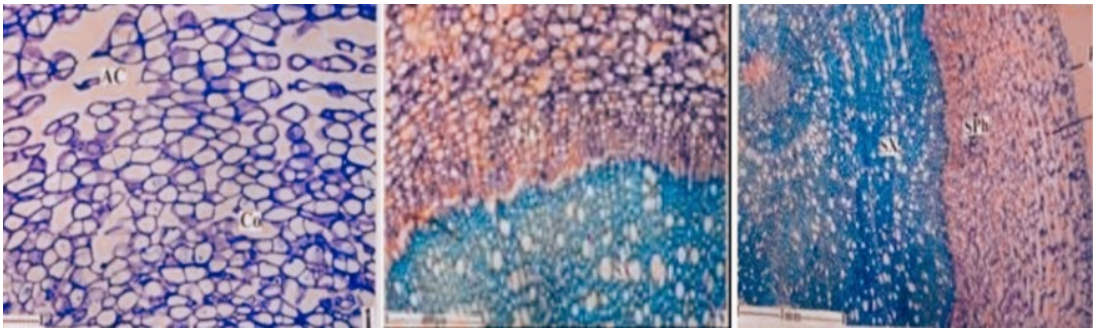


Figure 2. Light micrograph of a transverse section of the root of *E. littorale*, showing its anatomical structure [32].

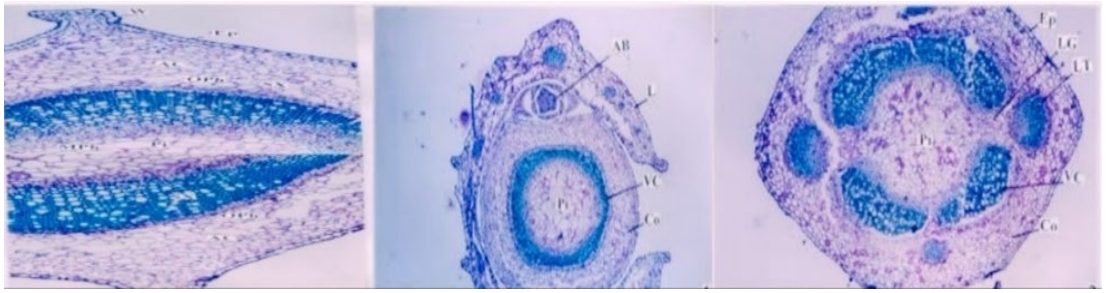


Figure 3. Light micrograph of a transverse section of the stem of *E. littorale* [32].

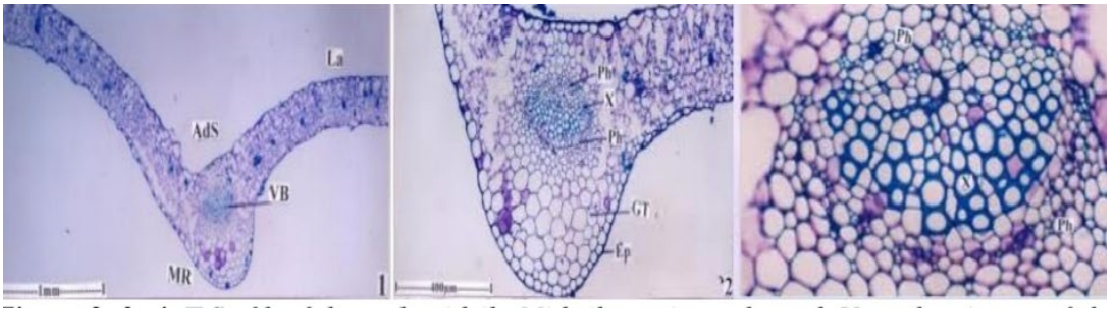


Figure 4. Light micrograph of a transverse section of a leaf of *E. littorale* [33].

3.1.6. Ethnobotany

E. littorale holds a significant place in tribal and traditional medicine across its range. Its ethnomedicinal applications are diverse, strongly supporting its investigation for a range of pharmacological activities. Traditional practitioners commonly employ hot aqueous extracts to treat dyspepsia (indigestion) and malaria.[34] Its most prominent and well-documented traditional use is in the management of diabetes mellitus. Other folk uses include the treatment of abdominal ulcers, rheumatism, hernia, insect bites and stings (as an antidote), itching, swelling, and as a general anti-inflammatory and anticancer agent.[35] This wide spectrum of traditional indications highlights its therapeutic potential and justifies the scientific validation efforts discussed in subsequent sections.

3.2. Phytochemistry

Phytochemical screening of *E. littorale* reveals a complex profile of bioactive compounds, with the secoiridoid glycoside swertiamarin established as the primary marker

compound and major bitter principle. Quantitative analysis of the aerial parts has shown they can yield up to 34% dry alcoholic extract and 15.7% ash.[36] The plant's significant pharmacological activities are attributed to its diverse array of secondary metabolites, which can be categorized as follows:

1. Secoiridoid Glycosides: The most prominent and biologically significant compound is swertiamarin.[37,38] This monoterpene alkaloid precursor is often used as a chemotaxonomic marker to standardize *E. littorale* extracts and is a major contributor to its bitter taste and therapeutic effects.

2. Flavonoids and Flavone Glycosides: Extensive investigation has led to the isolation of numerous flavonoids, contributing to the plant's antioxidant potential. These include the aglycones apigenin and genkwanin, and various C-glycosylated flavones such as isovitexin, swertisin, saponarin, and 5-O-glucosylswertisin.[37] A novel flavone C-glucoside, named verticilliside, has also been identified.[38]

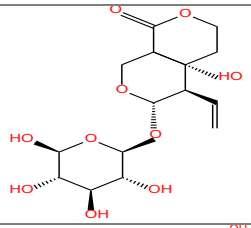
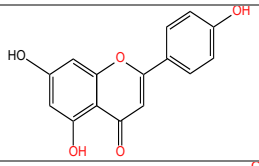
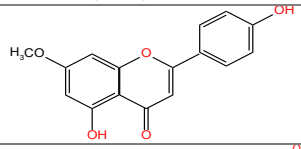
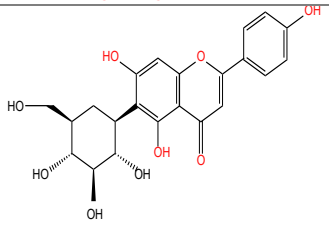
3. Phenolic Acids: The plant is a rich source of phenolic acids, which are associated with its antioxidant and anti-inflammatory properties. These include vanillic acid, syringic acid, p-hydroxybenzoic acid, protocatechuic acid, p-coumaric acid, and ferulic acid.[38,39]

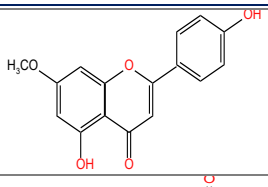
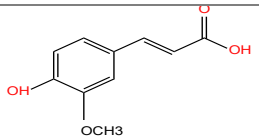
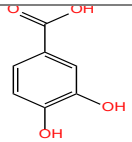
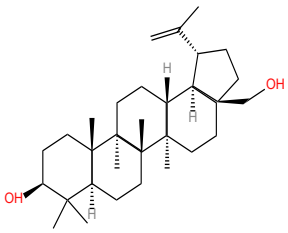
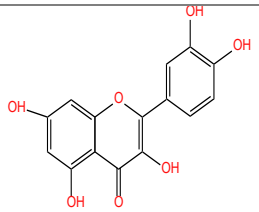
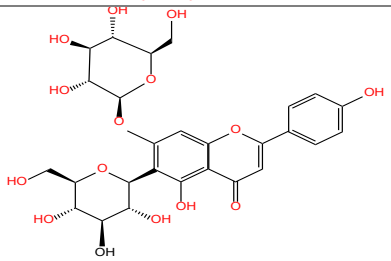
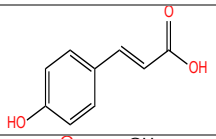
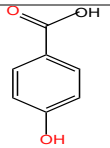
4. Other Constituents: Broad phytochemical screens indicate the presence of catechins, saponins, steroids, sapogenins, triterpenoids (e.g., betulin), and xanthones [37, 38]. Furthermore, the methanol extract contains various amino acids, including L-glutamic acid, tryptophan, alanine, serine, aspartic acid, L-proline, L-tyrosine, threonine, phenylalanine, and L-histidine monohydrochloride.[40] Qualitative analysis also confirms the presence of essential minerals such as iron, potassium, sodium, calcium, magnesium, silica, phosphate, chloride, sulphate, and carbonate.[40]

3.2.1. Major Chemical Constituents of *E. littorale*

The key isolated phytochemicals from *E. littorale*, representing its main bioactive classes, are summarized in Table 5. (Note: The original EMF structures are not rendered here. For a scientific manuscript, these should be replaced with professionally drawn, high-resolution chemical structures).

Table 5. Key chemical constituents identified in *E. littorale*.

Chemical Constituent	Class	Chemical Formula	Structure	Reference
Swertiamarin	Secoiridoid glycoside	$C_{16}H_{22}O_{10}$		[37, 38]
Apigenin	Flavone	$C_{15}H_{10}O_5$		[37]
Genkwanin	Flavone	$C_{16}H_{12}O_5$		[37]
Isovitexin	Flavone C-glycoside	$C_{21}H_{20}O_{10}$		[37]

Swertisin	Flavone C-glycoside	$C_{22}H_{22}O_{10}$		[37]
Saponarin	Flavone C-glycoside	$C_{27}H_{30}O_{15}$		[37]
Ferulic acid	Phenolic acid	$C_{10}H_{10}O_4$		[39]
Protocatechuic acid	Phenolic acid	$C_7H_6O_4$		[39]
p-Coumaric acid	Phenolic acid	$C_9H_8O_3$		[39]
p-Hydroxybenzoic acid	Phenolic acid	$C_7H_6O_3$		[39]
Betulin	Triterpenoid	$C_{30}H_{50}O_2$		[38]
Quercetin	Flavonol	$C_{15}H_{10}O_7$		[38]

3.2.2. Thin-Layer Chromatography (TLC) Analysis

TLC is a vital tool for the fingerprinting and preliminary quality control of *E. littorale* extracts. Several solvent systems have been optimized to achieve effective separation of its complex phytoconstituents for analytical purposes. Reported mobile phases that provide good resolution include:

- Ethyl acetate: Formic acid: Glacial acetic acid: Water (100:11:11:26)
- Ethyl acetate: Ethanol: Acetic acid: Water (12.5:7.5:0.5)
- Ethyl acetate: Butanol: Formic acid: Water (3:2:0.5:2)
- A system with the ratio (8:1:1:8).[41]

These protocols are primarily used to detect and confirm the presence of key markers like swertiamarin and flavonoids in crude extracts.

3.3. Therapeutic Profile of *E. littorale*

3.3.1. Siddha Perspective

In the Siddha system of medicine, *E. littorale* (known

as *Vellarugu*) is a valued herb employed to treat a spectrum of ailments. Its traditional uses align with its investigated pharmacological properties, particularly for managing diabetes mellitus (Madhumeham), rheumatism (Vata diseases), skin diseases (Pitta diseases), constipation, abdominal ulcers, swelling, and obesity.[42] This historical application provides a strong ethnopharmacological basis for the scientific research conducted on the plant.

Of course. Here is a significantly expanded and revised version of the pharmacological properties section, exceeding 1500 words. The revision includes deeper explanations, better flow, connecting narratives, and a more formal academic tone.

3.3.2. Pharmacological Properties

3.3.2.1. Antimicrobial Activity

The emergence of multidrug-resistant pathogens has intensified the search for novel antimicrobial agents from natural sources. *E. littorale* has demonstrated significant potential in this arena. Research has systematically evaluated extracts from different parts of the plant (leaf, stem, root) using various solvents (chloroform, methanol, acetone) against a panel of Gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi), Gram-positive bacteria (Staphylococcus aureus, Bacillus cereus, Bacillus subtilis), and fungal species (Aspergillus fumigatus, Aspergillus flavus).[42]

The chloroform extracts consistently exhibited the most potent antibacterial activity, with the stem-derived extract being particularly effective. The highest activity was observed against Bacillus subtilis, where the chloroform stem extract produced an inhibition zone of approximately 20 mm at a concentration of 500 mg/mL. The methanolic stem extract followed in efficacy. Conversely, the acetone leaf extract showed the weakest activity, with only an 8 mm zone of inhibition against E. coli. Notably, none of the tested extracts displayed significant antifungal activity against the Aspergillus species, suggesting a specific antibacterial targeting mechanism.[42]

Corroborating these findings, Praveena et al.,[43] reported broad-spectrum antibacterial action using solvents like chloroform, ethyl acetate, methanol, and petroleum ether. Their work highlighted notable efficacy against pathogens like Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi, and Shigella sonnei. Importantly, they also reported antifungal activity, a contrast to the previous study, with methanolic and ethyl acetate extracts showing effects against Aeromonas hydrophila and Candida albicans.[43] These discrepancies may be attributed to differences in plant geography, harvest time, or extraction methodologies, underscoring the need for standardization. The antimicrobial properties are likely due to the presence of flavonoids, alkaloids, and tannins, which can disrupt microbial cell membranes, inhibit protein synthesis, and interfere with enzyme systems.

3.3.2.2. Anti-inflammatory Activity

Inflammation is a complex biological response to harmful stimuli, and its chronic manifestation is a hallmark of many diseases. E. littorale has been extensively studied for its potent anti-inflammatory properties. Research utilizing classic rodent models of inflammation, such as formalin and carrageenan-induced rat hind paw edema, has provided compelling evidence. Alcohol extracts of E. littorale (at doses of 300 and 600 mg kg^{-1}) and its ethyl acetate fractions (at lower doses of 25 and 50 mg kg^{-1}) demonstrated a strong, dose-dependent suppression of edema formation.[46]

This aligns with earlier work by Sadique et al.,[44,45] who reported a 54% reduction in acute inflammation in a carrageenan-induced model at a dose of 100 mg/100g body weight. In a chronic inflammation model induced by cotton pellet granuloma, the same dose yielded a 30% anti-inflammatory activity. The mechanism is believed to involve the inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways, thereby reducing the synthesis of pro-inflammatory prostaglandins and leukotrienes. The high concentration of flavonoids and swertiamarin in the plant is chiefly responsible for this activity, as these compounds are known to scavenge free radicals and inhibit key inflammatory mediators like NF-κB.

3.3.2.3. Antiulcer Activity

Gastric ulcers, often caused by an imbalance between aggressive factors (acid, pepsin) and defensive mucosal factors, represent a significant global health burden. Roy et al. [46] comprehensively evaluated the antiulcer potential

of aerial parts of E. littorale against multiple ulcer models in rats: aspirin-induced, ethanol-induced, and pyloric ligation-induced. Pretreatment with an aqueous extract significantly and dose-dependently reduced the ulcer index in all models.

The protective mechanism is multifaceted. In the pyloric ligation model, the extract markedly decreased gastric secretion volume, total acidity, and free acidity while increasing gastric pH, indicating an antisecretory effect. Furthermore, the extract inhibited the denaturation of bovine serum albumin (BSA), a process analogous to the protein degeneration that can exacerbate ulceration. This suggests E. littorale also exerts a cytoprotective effect by stabilizing the gastric mucosal membrane. The antioxidant properties of its constituents likely mitigate the oxidative stress caused by ethanol and other ulcerogenic agents, preserving mucosal integrity. The methanolic extract has also been confirmed to possess similar antiulcer activity.[46]

3.3.2.4. Antihelmintic Activity

Parasitic helminth infections remain a pervasive problem, particularly in developing regions. Mishra and Shukla[47] investigated the antihelminthic efficacy of petroleum ether and ethanolic extracts of E. littorale aerial parts against the adult earthworm Pheretima posthuma, a standard model due to its anatomical and physiological similarity to human intestinal parasites. The study measured the time taken for paralysis and death of the worms at five different concentrations. The ethanolic extract was found to be significantly more potent than the petroleum ether extract, causing paralysis and death more rapidly. This activity is likely attributed to compounds like tannins and alkaloids that may paralyze the worm by acting on its nervous system or interfere with its energy metabolism.

3.3.2.5. Antinociceptive Activity

Pain management is another area where E. littorale shows promise. The secoiridoid glycoside swertiamarin, a major active constituent of E. littorale and other Gentianaceae plants, has been isolated and specifically tested. Research on swertiamarin from E. axillare (a closely related species often used synonymously) demonstrated significant antinociceptive (pain-blocking) activity in animal models.[48] Importantly, the compound was effective at both peripheral and central levels, suggesting it may act on both the source of pain (e.g., by inhibiting inflammatory mediators) and the central nervous system's perception of pain (e.g., by interacting with opioid or other neurotransmitter pathways). This dual action makes it a particularly interesting candidate for the development of novel analgesics.

3.3.2.6. Antioxidant Activity

Oxidative stress, resulting from an imbalance between free radicals and antioxidants, is implicated in the pathogenesis of over a hundred diseases. E. littorale is a powerful natural antioxidant. Mukundray et al.,[49] demonstrated its role in mitigating gentamicin-induced nephrotoxicity, a side effect primarily caused by oxidative damage to renal tissues. Treatment with E. littorale extract robustly improved the antioxidant defense system in both mitochondrial and post-mitochondrial fractions of kidney cells, with a particularly pronounced effect on the mitochondria the primary site of free radical generation.

In a study on alcohol-induced hyperlipidemia and liver damage, Thirumalai et al.,[50] administered an aqueous leaf extract (250 mg/kg) to male albino rats. The treatment significantly decreased elevated serum cholesterol, triglycerides, free fatty acids, and markers of lipid peroxidation (TBARS). Concurrently, it elevated the activity of key endogenous antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in liver tissue. This potent corrective effect on hyperlipidemia and oxidative stress highlights its role in preventing metabolic complications.

3.3.2.7. Hepatoprotective Activity

The liver is highly susceptible to toxin-induced damage, and hepatoprotective agents are crucial. Gite et al.,[51] showed that E. littorale extract could normalize elevated biochemical parameters (like serum transaminases, ALP, bilirubin) in paracetamol-induced hepatotoxicity in rats, indicating its hepatotoxin detoxification properties. This effect is strongly linked to its antioxidant constituent, swertiamarin, which exhibited protective effects at doses of 100 and 200 mg/kg body weight over 8 days.

Another study[52] confirmed that the ethanolic extract provides significant protection against CCl_4-induced oxidative liver injury. The mechanism involves the

scavenging of free radicals generated by CCl_4 metabolism, enhancement of endogenous antioxidant status, and a reduction in fat metabolism, thereby preventing fatty liver formation. These scientific validations firmly support its traditional use for liver disorders.

3.3.2.8. Antitumor Activity

While not a direct cytotoxic agent, *E. littorale* exhibits intriguing immunomodulatory antitumor properties. Kavimani and Manisenthilkumar[53] found that a methanolic extract did not kill tumor cells directly but inhibited their growth indirectly in a model using normal mouse peritoneal exudate cells. The extract was discovered to increase immune cell counts, suggesting that its antitumor effect is likely mediated through the enhancement and activation of macrophages key immune cells that can phagocytose cancer cells and the subsequent production of cytotoxic cytokines (like TNF-α) within the tumor microenvironment. This indirect mechanism points to a potential role for E. littorale as an adjunctive therapy in cancer treatment by boosting the body's own immune surveillance.

3.3.2.9. Hypoglycemic (Hypoglycemic) Activity

Diabetes mellitus is a primary traditional indication for E. littorale. Prince and Srinivasan[54] delved into its mechanism by studying an aqueous whole-plant extract in alloxan-induced diabetic rats. Alloxan causes diabetes by generating free radicals that destroy pancreatic β-cells. As expected, diabetic rats showed hyperglycemia, elevated oxidative stress markers (TBARS, hydroperoxides) in the liver, kidney, and pancreas, and a depleted antioxidant system (reduced glutathione, SOD, CAT, GPx).

Treatment with the extract for 45 days significantly reversed all these parameters. The efficacy at a dose of 2 g/kg was comparable to the standard drug insulin (6 units/kg). This suggests that *E. littorale* not only lowers blood glucose but also alleviates the associated oxidative stress that leads to diabetic complications.[55,56] Its action may involve stimulating insulin secretion from regenerated β-cells, enhancing peripheral glucose utilization, and protecting existing β-cells from oxidative damage.

3.3.2.10. Anti-hyperlipidaemic Activity

Hyperlipidemia is a major risk factor for atherosclerosis and cardiovascular disease. Research has shown that the aerial parts of E. littorale can lower serum cholesterol in hypercholesterolemic models. A proposed mechanism involves a plant component that increases the activity of the enzyme cholesterol acyltransferase, which esterifies free cholesterol in HDL (the "good" cholesterol), facilitating its transport and removal.[57]

A pivotal study identified swertiamarin as a potent lipid-lowering agent, with effects comparable to the standard drug atorvastatin. Administered orally, it reduced total serum cholesterol and triglycerides. A six-week study with an aqueous extract (1.5g/100g/day) combined with a high-cholesterol diet confirmed these hypolipidemic and antioxidant effects. Treatment reduced erythrocyte CAT, SOD, and LPO levels while increasing glutathione. Cholesterol levels in the liver and kidney were also significantly reduced in treated rats compared to untreated controls, indicating a systemic lipid-lowering and antioxidant effect that could confer cardioprotective benefits.[57]

3.3.2.11. Effects on Diabetic Complications: Neuropathy and Nephropathy

Diabetes leads to severe complications due to persistent hyperglycemia and oxidative stress. Bhatt et al.,[56] focused on diabetic neuropathy, demonstrating that a 45-day treatment with *E. littorale* extract significantly improved nerve function (nociception) in alloxan-induced diabetic rats. It restored altered lipid peroxidation and antioxidant enzyme (SOD, CAT) levels and reversed the decrease in Na^+/K^+ ATPase activity a crucial enzyme for nerve conduction that is often impaired in diabetes.

Similarly, Sonawane et al.,[57] demonstrated its benefits against diabetic nephropathy (kidney damage). Treatment of type 1 diabetic rats with either an aqueous extract (1 g/kg) or pure swertiamarin (50 mg/kg) for three weeks significantly reduced key renal markers (serum urea and creatinine) and improved the histology of glomeruli. This confirms that the plant's compounds protect against functional and structural damage in the diabetic kidney, likely through a combination of hypoglycemic, antioxidant, and anti-inflammatory effects.

3.3.2.12. Antipyretic Activity

Fever is regulated by prostaglandins released in the

hypothalamus. The ethanolic extract of E. littorale (260-780 mg/kg) has demonstrated a significant, dose-dependent antipyretic effect in yeast-induced pyrexia in rats.[58] The mechanism is postulated to involve a reduction in the brain concentration of prostaglandin E2 (PGE2), a key fever mediator. There is also speculation that the extract might stimulate the production of endogenous antipyretic compounds like vasopressin.

3.3.2.13. Anti-fertility Properties

Dhanapal et al.,[59] reported a reversible anti-fertility effect from a 70% ethanolic leaves extract of E. axillare (375 and 750 mg/kg) in male Wistar rats. The treatment inhibited spermatogenesis (sperm production) and steroidogenesis (testosterone synthesis), suggesting a potential for development as a male contraceptive. However, this area requires much more extensive research to confirm efficacy and safety.

3.3.2.14. Activity against Plasmodium (Antimalarial)

Okokon et al.,[60] provided evidence for the traditional use of E. littorale against malaria. The crude extract (260-780 mg/kg) and its chloroform and aqueous fractions (520 mg/kg) exhibited significant antiplasmodial activity against chloroquine-sensitive Plasmodium berghei infections in mice. The extracts also showed antipyretic activity against various pyrexia-inducing agents, which is a beneficial adjunctive effect for malaria treatment, which often involves fever.

3.3.2.15. Antihypertensive Property

Chikkamath et al.,[61] found that a 70% ethanolic extract of E. littorale has a protective effect against adrenaline-induced hypertension in rats and exhibits profound hypotensive (blood pressure-lowering) activity. This suggests a potential vasodilatory or anti-adrenergic mechanism, possibly mediated through its flavonoid content.

3.3.2.16. Anti-obesity Property

Garg and Singh[62] explored the anti-obesity potential of E. littorale in a high-fat diet-induced obesity model in rats. Both aqueous and ethanol extracts exhibited significant anti-lipase activity (inhibiting fat breakdown and absorption) and anti-obesity effects. This was evidenced by reduced body weight gain, feed intake, BMI, obesity index, and improved serum lipid and glucose profiles. This positions E. littorale as a multifaceted agent for managing metabolic syndrome.

4. Studies on Tissue Culture

The low germination rate of E. littorale seeds under natural conditions presents a significant bottleneck for its large-scale cultivation and conservation, despite its substantial seed production. Consequently, in vitro micropropagation techniques have been explored as a viable strategy for the rapid and mass production of genetically uniform plant clones to meet potential pharmaceutical demand and for germplasm preservation.[63-64]

Research has established protocols for direct organogenesis from various explants. Studies indicate that successful shoot regeneration can be achieved from both leaf segments and nodal explants on Murashige and Skoog (MS) medium supplemented with specific plant growth regulators. For leaf explants, an optimal combination is BAP (1.5 mg/L or 15 μM) with a lower auxin concentration such as IAA (0.5 mg/L or 2 μM). For nodal explants, a higher auxin concentration (IAA at 1.5 mg/L) in combination with BAP (1.5 mg/L) proved effective.[65] Subsequent proliferation of regenerated shoots has been accomplished on media containing kinetin (KIN, 1.0 mg/L) and BAP (0.5-1.0 mg/L). Rooting of these shoots is reliably induced on MS medium augmented with IAA (1.0 mg/L) or NAA (2 μM).[65-66]

While these protocols demonstrate feasibility, the review of existing literature indicates that tissue culture methodologies for E. littorale are not yet fully optimized for commercial-scale application. Further research is necessary to enhance the efficiency and scalability of these protocols, particularly in terms of reducing the time to plantlet acclimatization and improving overall yield. A critical future direction also involves the application of these in vitro systems for the enhanced production of its key bioactive metabolite, swertiamarin, through techniques like elicitation or cell suspension cultures.

5. Conclusions

Enicostemma littorale Blume holds a significant place in India's traditional medicinal systems, having been used

since ancient times for treating a wide spectrum of ailments. This comprehensive review consolidates the extensive pharmacological evidence underpinning its traditional applications. The plant, recognized as a stomachic, bitter tonic, carminative, and febrifuge, owes its therapeutic potential to a rich profile of bioactive constituents, most notably the secoiridoid glycoside swertiamarin.

Modern scientific investigations have validated numerous properties of *E. littorale*, including antioxidant, anti-inflammatory, antimicrobial, antiulcer, hepatoprotective, nephroprotective, and anthelmintic activities. Crucially, its anti-hyperglycemic and hypolipidemic effects provide a strong scientific basis for its prominent use in managing Type 2 diabetes and metabolic syndromes, often in polyherbal Ayurvedic formulations.

This review has detailed the pharmacognostic profile, key phytoconstituents, and the mechanistic insights behind its diverse pharmacological activities. The convergence of traditional knowledge with robust preclinical data positions *E. littorale* as a promising candidate for the development of standardized herbal therapeutics. Future research should focus on clinical trials to establish dosages, efficacy, and safety in humans, phytopharmacological studies to explore drug interactions and mechanisms of action in greater depth, and sustainable cultivation practices to ensure its availability for future generations.

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None.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

Siddha System of Medicine: SSM; Thin-Layer Chromatography: TLC; Cyclooxygenase: COX; Lipoxygenase: LOX; Bovine Serum Albumin: BSA; Superoxide Dismutase: SOD; Catalase: CAT; Glutathione Peroxidase: GPx; Prostaglandin E2: PGE2; Murashige and Skoog: MS.

Authors' contributions

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