

**Review Article****Evaluation of the Anti-Diabetic and Renoprotective Effects of Enicostemma Littorale Whole Plant Extract in Fructose-Induced Insulin Resistance Model in Rats****Vipul Raj<sup>1</sup>, Nowshaba Perween<sup>2</sup>, Badal Singh<sup>3</sup>, Mamta Kumari<sup>4</sup>, Anjali Kumari<sup>5</sup>,  
Shashi Saxena<sup>6</sup>**<sup>1,2,3,4,5</sup>Students of Mahadeva Lal Schroff College of Pharmacy Aurangabad Bihar<sup>6</sup>Assistant Professor of Mahadeva Lal Schroff College of Pharmacy Aurangabad Bihar**Article Info: Received: 10-03-2026 / Revised: 14-04-2026 / Accepted: 30-04-2026****Corresponding Author: Vipul Raj****DOI: <https://doi.org/10.32553/jbpr.v15i3.1479>****Conflict of interest statement: No conflict of interest****Abstract:**

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, action, or both, leading to severe complications such as diabetic nephropathy. Despite the availability of synthetic antidiabetic drugs, their limitations, including adverse effects and incomplete control of complications, necessitate the exploration of safer and more effective alternatives. Medicinal plants have emerged as promising therapeutic agents due to their bioactive phytochemicals with multifaceted pharmacological properties. This study focuses on evaluating the efficacy of *Enicostemma littorale*, a traditionally used medicinal herb, in improving insulin sensitivity and providing renal protection in fructose-induced insulin-resistant rat models. The plant is rich in bioactive constituents such as flavonoids, alkaloids, phenolics, and terpenoids, which contribute to its antidiabetic, antioxidant, and anti-inflammatory activities. The proposed work includes extraction, phytochemical screening, in vitro antioxidant assessment, and in vivo evaluation of biochemical parameters such as blood glucose, insulin levels, lipid profile, and histopathological examination of kidney tissues. Evidence from previous studies suggests that *Enicostemma littorale* enhances insulin secretion, reduces oxidative stress, inhibits inflammatory pathways, and improves renal function markers. Therefore, this study aims to validate the dual therapeutic potential of *Enicostemma littorale* in managing type 2 diabetes and diabetic nephropathy, providing a scientific basis for its future development as a safe, plant-based therapeutic agent.

**Keywords:** Diabetes Mellitus, Insulin Resistance, Diabetic Nephropathy, *Enicostemma littorale*, Phytochemicals, Antidiabetic Activity, Renoprotection, Oxidative Stress, Herbal Medicine, Antioxidant Activity.

**Chapter 1: Introduction****Diabetes Mellitus**

Diabetes mellitus (DM) is a serious, chronic, and complex metabolic disorder of multiple aetiologies with profound consequences, both acute and chronic [1]. Also known only as diabetes, DM and its complications affect people

both in the developing and developed countries, leading to a major socioeconomic challenge. It is estimated that 25% of the world population is affected by this disease. Genetic and environmental factors contribute significantly to the development of diabetes. During the development of diabetes, the cells of the body

cannot metabolize sugar properly due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin (a peptide hormone that regulates blood glucose). The inability of insulin to metabolize sugar occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. This triggers the body to break down its own fat, protein, and glycogen to produce sugar, leading to the presence of high sugar levels in the blood with excess by-products called ketones being produced by the liver. Diabetes is distinguished by chronic hyperglycemia with disturbances in the macromolecules' metabolism as a result of impairments in insulin secretion, insulin action, or both. Diabetes causes long-term damage, dysfunction, and failure of various organ systems (heart, blood vessels, eyes, kidneys, and nerves), leading to disability and premature death. The severity of damage triggered by hyperglycemia on the respective organ systems may be related to how long the disease has been present and how well it has been controlled. Several symptoms such as thirst, polyuria, blurring of vision, and weight loss also accompany diabetes [2].

### **Types of diabetes:**

There are two types of diabetes:

- Type 1 DM (T1DM)
- Type 2 DM (T2DM)

The T1DM is also known as insulin-dependent diabetes. It is primarily due to pancreatic islet beta cell destruction and is characterized by deficient insulin production in the body. Patients with T1DM are prone to ketoacidosis and need daily administration of insulin to control the amount of glucose in their blood. The majority of T1DM occurs in children and adolescents [3].

The T2DM, also known as non-insulin-dependent diabetes, results from the body's ineffective use of insulin and hyperglycemia and accounts for the vast majority of people with diabetes around the world. Insulin resistance is due to a reduced responsiveness of target tissues to normal circulating levels of insulin [4].

Ethnicity, family history of diabetes, and previous gestational diabetes, older age, overweight and obesity, unhealthy diet, physical inactivity, and smoking increase diabetes risk. Most people with diabetes are affected by T2DM diabetes (90%), usually occur nearly entirely among adults but, in these days, is increasing in children [5].

### **Prevalence of diabetes:**

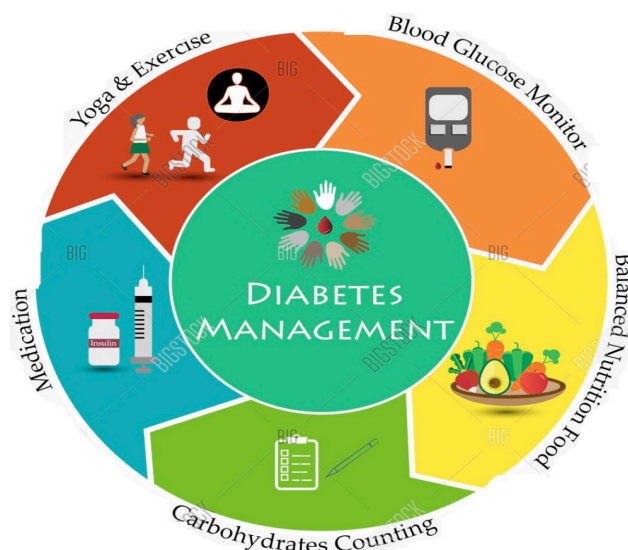
The universal prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. Moreover, the prevalence of diabetes has also been found to steadily increase for the past 3 decades and has risen faster in low- and middle-income countries compared to high-income countries. The increase in the prevalence of diabetes is parallel with an increase in associated risk factors such as being overweight or obese. If not properly treated or controlled, diabetes may cause blindness, kidney failure, lower limb amputation, and other long-term consequences that impact significantly on the quality of life [6]. Interestingly, the WHO also projects that diabetes will be the seventh leading cause of death in 2030. The incidence and prevalence of diabetes have continued to increase globally, despite a great deal of research with the resulting burden resting more heavily on tropical developing countries. Based on demographic studies, by 2030, the number of people older than 64 years with diabetes will be greater in developing countries ( $\geq 82$  million) in comparison to that in developed countries ( $\geq 48$  million). The greatest relative increases are projected to occur in the Middle East crescent, sub-Saharan Africa, and India [7].

### **Management of diabetes:**

Amongst all people with diabetes, T2DM accounts for the majority (90%) of cases, and these can be prevented as well as treated easily, while T1DM cannot be prevented with current knowledge. Since management of diabetes is complex and multidisciplinary, it should include primary prevention through promotion of a healthy diet and lifestyle (such as exercise).

Dietary management and exercise represent important pillars of care and are crucial in the treatment of T2DM, and both may be adequate

to attain and retain the therapeutic goals to normolipidemic and normoglycemia<sup>8</sup>.



### Antidiabetic drugs and their side effects:

There are several classes of oral hypoglycemic drugs that exert antidiabetic effects through different mechanisms, namely sulfonylureas, biguanides,  $\alpha$ -glucosidase inhibitors, thiazolidinediones, and non-sulfonylureas secretagogues. Oral sulfonylureas, such as glimepiride and glyburide, act to reduce blood sugar, mainly by elevating insulin release from islets of Langerhans. This is achieved through binding with the sulfonylurea receptor on  $\beta$  cells resulting in adenosine triphosphate-dependent potassium channels closure. As a result, the cell membrane depolarizes and the following calcium influx accompanied by secretion of stored insulin from secretory granules within the cells takes place. This mechanism works only in the presence of insulin [9].

Another oral hypoglycemic drug, the biguanides, acts to reduce hepatic gluconeogenesis and to replenish peripheral tissues' sensitivity to insulin, actions that are achieved through elevation of insulin-stimulated uptake and use of sugar. Nevertheless, biguanides are ineffective in insulin absence. The best example of this class is metformin [10].

The  $\alpha$ -glucosidase inhibitors, such as acarbose and miglitol, impede certain enzymes responsible for the breakdown of carbohydrates in the small intestine. This class of hypoglycemic agents acts mostly by reducing the absorption rate of carbohydrates in the body. Also, acarbose reversibly inhibits both pancreatic  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes by binding to the carbohydrate-binding region and by interfering with their hydrolysis into monosaccharides, which leads to a slower absorption together with a reduction in postprandial blood sugar levels [11].

Another important class of oral hypoglycemic agents is the thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, of which the mechanism of action primarily includes improving muscle and adipose tissue sensitivity to insulin and, to a smaller extent, reducing liver glucose production. TZDs also are potent and selective agonists to the nuclear peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) present in liver, skeletal muscle, and adipose tissue. Activation of PPAR $\gamma$  receptors controls the transcription of insulin-responsive genes involved in the regulation of transportation, production, and glucose use. Also, TZDs have been reported to augment  $\beta$ -cell function by

lowering free fatty acid levels that ultimately lead to  $\beta$ -cell death [12].

The last class of oral hypoglycemic agents is the non-sulfonylureas secretagogues, which include meglitinide and repaglinide and which increases the secretion of insulin from active  $\beta$  cells by a similar mechanism as sulfonylureas. However, this class of oral antidiabetic agents binds to different  $\beta$ -cell receptors [13].

Although synthetic oral hypoglycemic drugs alongside insulin are the main route for controlling diabetes, they fail to reverse the course of its complications completely and further worsen it by the fact that they also demonstrate prominent side effects. This forms the main force for discovering alternative sources of antidiabetic agents. Despite the significant progress made in the treatment of diabetes using oral antidiabetic agents in the past three decades, the results of treatment of diabetic patients are still far from perfect. Several disadvantages have been reported related to the use of those oral hypoglycemic agents, including drug resistance (reduction of efficiency), adverse effects, and even toxicity. For example, sulfonylureas lose their effectiveness after 6 years of treatment in approximately 44% of patients, whereas glucose-lowering drugs are reported to be not able to control hyperlipidemia. Due to the several limitations associated with the use of existing synthetic antidiabetic drugs, the search for newer antidiabetic drugs from natural source continues [14].

#### **Diabetic nephropathy:**

Diabetes causes a variety of serious complications, of which Diabetic Nephropathy is a serious health problem worldwide and occurs in about 40% of people with diabetes. Diabetic Nephropathy increases the mortality rate of patients with diabetes, although deaths from complications of diabetes are mostly caused by cardiovascular problems. Diabetic Nephropathy has five stages, namely, hyperfiltration, normoalbuminuria, microalbuminuria, macroalbuminuria, and ESRD [15]. ESRD may occur when Diabetic

Nephropathy ultimately results in kidney damage via hyperfiltration, increased albumin excretion, microalbuminuria, nodular and diffuse glomerulosclerosis, and proteinuria. Furthermore, chronic hyperglycemia causes structural abnormalities including tubular atrophy, glomerular basement membrane-stiffening, kidney enlargement, hypertension, edema, and progressive renal dysfunction in the later stages of ESRD. Number of patients with ESRD increases with diabetic nephropathy cases. Therefore, dialysis or kidney transplantation is urgently needed for patient survival [16].

Diabetic nephropathy is characterized by the structural abnormalities of kidney tissues, such as glomerular enlargement, advancement of mesangial matrix, and stiffening of tubular and glomerular basement membranes. Patients with Diabetic nephropathy have abnormal levels of urea, albumin, creatinine, uric acid, and blood urea nitrogen (BUN) in their serum and experience fluid retention, glomerular lesions, and glomerular filtration rate (GFR) reduction [17]. Several causative factors of diabetic nephropathy have been proposed, including oxidative stress enhancement, mitogen-activated protein kinases, polyol pathways, protein kinase C (PKC), and poly (ADPribose) polymerase activation, advanced glycation end product (AGE) production, inflammatory mediators (TNF- $\alpha$ , IL-2, IL1 $\beta$ , and IL-6), growth factors (VEGF and CTGF), and chemokine liberation. Among these factors, oxidative stress is believed to be a factor in the onset and progression of Diabetic nephropathy [18].

Diabetic nephropathy pathogenesis is incredibly complex and remains largely unknown; it implicates the direct action of excessive extracellular glucose in tubular, glomerular, interstitial, and vascular cells. As a result, the therapeutic outcomes for diabetic nephropathy are poor. Standard medication, including stringent blood pressure and sugar control, seems to be ineffective in arresting the development of diabetic nephropathy to ESRD

and Diabetic nephropathy-related mortality. Another treatment strategy for Diabetic nephropathy is the administration of insulin and antidiabetic drugs, including sulfonylureas, biguanides, thiazolidinediones, insulin sensitizers, inhibitors of  $\alpha$ -glycosidase, agonists of glucagon-like peptide, inhibitors of dipeptidyl peptidase-4, incretin-based drugs, and inhibitors of sodium-glucose cotransporter. These drugs are usually administered with attention to the GFR of the patient. However, this strategy only slows the disease's progression. Thus, the discovery of novel medications targeting diabetic nephropathy pathology including oxidative stress and inflammation has taken centre stage [19].

### **Bioactive phytochemicals for diabetic nephropathy**

Medicinal plants have many chemical compounds or phytochemicals that have various pharmacological activities [20]. The use of phytochemicals and their bioactive components as natural modifying agents in the cure of numerous ailments, including Diabetic nephropathy is supported by growing evidence of their positive health effects [21]. Medicinal plants contain major phytochemical compounds with health advantages, including alkaloids, phenolics, flavonoids, terpenoids, and miscellaneous compounds. These compounds are important in ameliorating Diabetic nephropathy progression.

**Alkaloids:** Alkaloids are basic chemical compounds (containing nitrogen) present in a wide range of species, such as fungi, bacteria, plants, and animals. Examples: Berberine, Magnoflorine, Oxymatrine, Trigonelline

**Phenolics:** Phenolic compounds comprise a group of compounds (secondary metabolites) generated by the phenylpropanoid metabolism of plant shikimic acid and

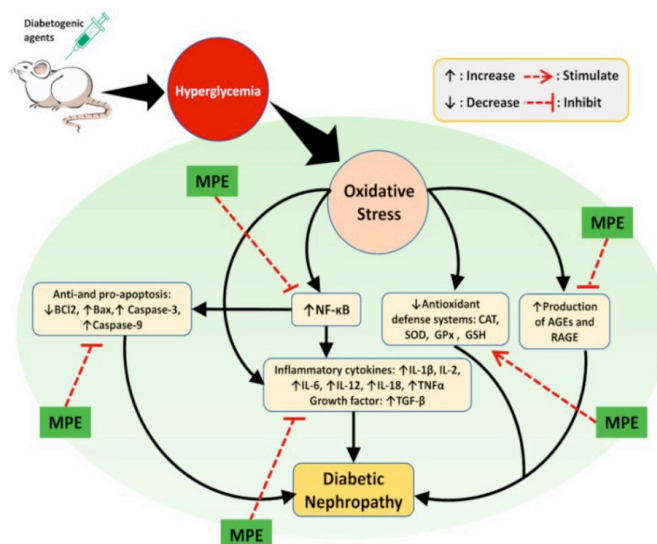
pentose phosphate. Their structure consists of benzene rings with hydroxyl substituents, and their complexity ranges from simple to complex polymers of phenolic compounds [22]. Examples: Resveratrol, Gallic acid, Syringaresinol, Mangiferin

**Flavonoids:** Among plant secondary metabolites, flavonoids are the most diverse groups. They are a type of phenolics with a flavone backbone (2-phenylchromen-4-one) and are present in many different foods and beverage items. Functional groups attached to the basic flavonoid structure define the subclasses of flavones, isoflavones, flavanols, flavonols, flavanones, and anthocyanins. Example: Hesperetin, Luteolin, Catechin, Genistein, Quercetin, Kaempferol

**Terpenoids:** Terpenoids, sometimes referred to as isoprenoids, are a group of chemical compounds derived from isoprene that are widely distributed throughout various plant, fungal, algal, and sponge taxa. Examples: Andrographolide, Astragaloside, Lupeol, Ursolic acid.

### **Renoprotective mechanisms of medicinal plants:**

Phytochemicals derived from medicinal plants are less harmful than medications made from synthetic substances. However, their precise bioactive components, mode of action, pharmacological properties, and potential risks are poorly understood [23]. Plant extracts exhibit renoprotective activity in various ways. The renoprotective activity of medicinal plant extracts are realized by reducing oxidative stress and suppressing inflammation, AGE production, cell apoptosis, and tissue injury-related protein expression. The complete information of the plants' scientific names, extract forms, animal models, extract doses, and possible modes of action.



**Figure 1: Possible mechanisms of action of plant extracts in diabetic nephropathy.**

Experimental animal were induced using diabetogenic agents such as STZ, alloxan, and HFD causing hyperglycemia which in turn causes oxidative stress. Oxidative stress in the kidney triggers the occurrence of diabetic nephropathy through increased inflammation, apoptosis, and production of AGEs. In addition, decreased levels of antioxidants can also cause diabetic nephropathy. Oxidative stress can increase the expression of NF-κB in the kidney so that it activates proinflammatory cytokines (IL-1 $\beta$ , IL-2, IL-6, IL-12, IL-18, and TNF $\alpha$ ) and produces growth factors (TGF- $\beta$ ). NF-κB also reduces the anti-apoptosis (Bcl2) factor and increases the pro-apoptosis (Bax, Caspase-3, and Caspase-9) factors. Decreased renal antioxidant levels (SOD, CAT, GPx, and GSH) as a result of oxidative stress exacerbate diabetic nephropathy progression since they can no longer protect the kidney from the adverse effects of ROS. An increase in the number of AGEs in kidney leads to inflammation as a result of the modification of lipids and proteins. Medicinal plant extracts (MPE) show a renoprotective effect on the diabetic nephropathy animal model via amelioration of the abovementioned causative factors.

### Medicinal Plants as an Alternative Source of Antidiabetic Agents

Natural products, particularly of plant origin, are the main quarry for discovering promising lead candidates and play an imperative role in the upcoming drug development programs. Ease of availability, low cost, and least side effects make plant-based preparations the main key player of all available therapies, especially in rural areas. Moreover, many plants provide a rich source of bioactive chemicals, which are free from undesirable side effects and possess powerful pharmacological actions. Plants also have always been an exemplary source of drug with many of currently available drugs being obtained directly or indirectly from them [24].

For centuries, many plants have been considered a fundamental source of potent antidiabetic drugs. In developing countries, particularly, medicinal plants are used to treat diabetes to overcome the burden of the cost of conventional medicines to the population. Nowadays, treatments of diseases including diabetes using medicinal plants are recommended because these plants contain various phytoconstituents such as flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides, which may possess antidiabetic activities [25].

The antihyperglycemic effects resulting from treatment with plants are usually attributed to their ability to improve the performance of pancreatic tissue, which is done by increasing

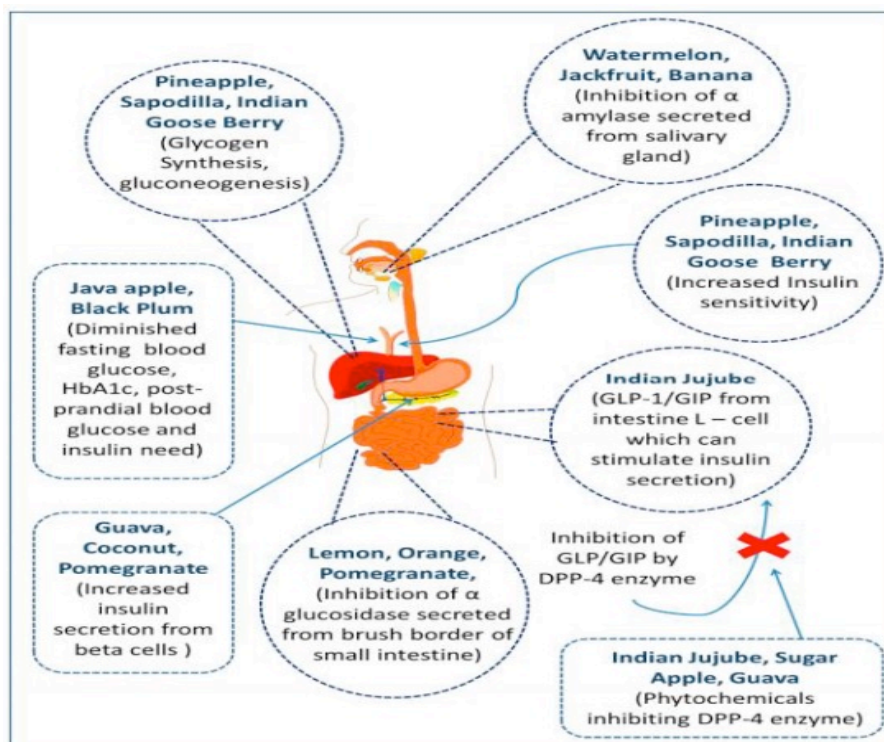
insulin secretions or by reducing the intestinal absorption of glucose.

The number of people with diabetes today has been growing and causing increasing concerns in the medical community and the public. Despite the presence of antidiabetic drugs in the pharmaceutical market, the treatment of diabetes with medicinal plants is often successful. Herbal medicines and plant components with insignificant toxicity and no side effects are notable therapeutic options for the treatment of diabetes around the world [26]. Most tests have demonstrated the benefits of medicinal plants containing hypoglycemic properties in diabetes management.

Medicinal plants (i.e., aloe, banaba, bitter melon, caper, cinnamon, cocoa, coffee, fenugreek, garlic, guava, gymnema, nettle, sage, soybean, green and black tea, turmeric, walnut, and yerba mate) used for treating diabetes and its comorbidities and the mechanisms of natural products as antidiabetic agents, with attention to compounds of high interest such as fukugetin,

palmatine, berberine, honokiol, amorfrutins, trigonelline, gymnemic acids, gurmarin, and phlorizin.

Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically in antidiabetic and antihyperlipidemic remedies. Antihyperglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., that are frequently implicated as having antidiabetic effect.



**Figure 2: Mechanism of actions of plants exert antidiabetic activity**

**Table No. 1: List of plants having antidiabetic activity [53].**

Plant part	Name of plants
Aerial parts	Artemisia pallens, Bidens pilosa, Bixa orellana, Teramnus labialis
Bark	Cinnamomum zeylanicum, Croton cajucara
Bulb	Allium cepa, Allium sativum
Flower	Cassia auriculata, Gentiana olivier, Musa sapientum
Fruit	Carum carvi, Coriandrum sativum, Embellica officinalis, Juniperus communis, Momordica charantia, Xanthium strumarium
Leaves	Aloe barbadensis, Annona squamosa, Averrhoa bilimbi, Azadirachta indica, Beta vulgaris, Camellia sinensis, Cassia alata, Eclipta alba, Eucalyptus globulus, Euphrasia officinale, Ficus carica, Gymnema sylvestre, Gynura procumbens, Ipomoea aquatica, Mangifera indica, Myrtus communis, Memecylon umbellatum, Morus indica, Ocimum
Rhizome	Nelumbo nucifera
Roots	Clausena anisata, Glycyrrhiza glabra, Helicteres isora, Pandanus odoros
Seed	Acacia arabica, Agrimony eupatoria, Lupinus albus, Luffa aegyptiaca, Lepidium sativum, Mucuna pruriens, Punica granatum
Stem	Amaranthus spinosus, Coscinium fenestratum
Tubers	Ipomoea batata
Whole plant	Abies pindrow, Achyranthus aspera, Ajauga iva, Aloe vera, Anacardium occidentale, Andrographis paniculata, Capsicum frutescens, Cryptolepis sanguinolenta, Encostemma littorale, Ficus religiosa

**Table No. 2: List of plants having insulin mimetic or insulin secretory activity [53].**

Plant botanical name	Common name	Family	Mechanism of action
Abies pindrow	Morinda	Pinaceae	Insulin secretagogue activity
Acacia arabica	Babool	Leguminosae	Release of insulin from pancreas
Agrimony eupatoria	Rosaceae		Insulin releasing and insulin like activity
Aloe barbadensis	Gheequar	Liliaceae	Stimulating synthesis and release of insulin
Annona squamosa	Sharifa	Annonaceae	Increased plasma insulin level
Averrhoa	Bilimbi	Oxalidaceae	Increase serum insulin level
bilimbi			
Bixa orellana	Annotta	Bixaceae	Increase plasma insulin concentration and increase insulin binding on insulin receptor
Boerhaavia diffusa	Punamava	Nyctaginaceae	Increase plasma insulin concentration

Camellia sinensis	Green tea	Theaceae	Increase insulin secretion
Capsicum frutescens	Mirch	Solanaceae	Increase insulin secretion and reduction of insulin binding on the insulin receptor
Cinnamomum zeylanicum	Dalchini	Dalchini	Dalchini Elevation in plasma insulin level
Clausena anisata	-	Rutaceae	Stimulate secretion of insulin
Eucalyptus globulus	Eucalyptus	Myrtaceae	Increase insulin secretion from clonal pancreatic beta line (BRIN-BD 11)
Ficus religiosa	Peepal	Moraceae	Initiating release of insulin
Hibiscus rosa	Gudhal	Malvaceae	Stimulate insulin secretion from beta cells
Helicteres isora	Indian screw tree	Sterculiaceae	Decrease plasma triglyceride level and insulin sensitizing activity
Ipomoea batata	Shakarkand	Convolvulaceae	Reduce insulin resistance and blood glucose level
Juniperus communis	Hauber	Pinaceae	Increase peripheral glucose consumption and induce insulin secretion
Olea europia	Olive	Oleaceae	19 Increase insulin release and increase peripheral uptake of glucose
Swertia chirayata	Chirayata	Gentianaceae	Stimulates insulin release from islets
Scoparia dulcis	Mithi patti	Scrophulariaceae	Insulin-secretagogue activity
Tinospora crispa	Giloe	Menispermaceae	Anti-hyperglycemic, stimulates insulin release from islets
Urtifca dioica	Bichhu booti	Urticaceae	Increase insulin secretion
Vinca rosea	Sadabahr	Apocynaceae	Beta cell rejuvenation, regeneration and stimulation
Zingiber officinale	Adrak	Zingiberaceae	Increase insulin level and decrease fasting glucose level

## Chapter 2: Literature Review

**Amit, et al (2025):** Reviewed Mamajjaka (*Enicostemma littorale* Blume), a perennial herb, holds a significant place in Ayurveda, known for its "Pramehaghna" (Antidiabetic) properties and its ability to

balance pitta and kapha doshas. This traditionally used for various ailments, including rheumatism, skin diseases, abdominal disorders, and fever. Studies have shown that *Enicostemma littorale* can reduce blood glucose and serum insulin levels in diabetic patients. The plant has been reported to enhance glucose-

induced insulin release from pancreatic islets, potentially through a K (+)-ATP channel-dependent pathway. Beyond its antidiabetic effects, *Enicostemma littorale* exhibits antioxidants, antiinflammatory, and antihyperlipidemic properties. Studies have identified various phytochemicals, including swer tiamarin, apigenin, and isovitexin, which may contribute to its antidiabetic activity. *Enicostemma littorale* is generally considered low toxicity, with studies indicating that it does not produce significant toxicity in rats. Studies have shown that heavy metals in *Enicostemma littorale* are below the WHO/FDA permissible limits. Clinical trials have shown the safety and antidiabetic activity of *Enicostemma littorale* in diabetic and prediabetic patients. The plant has been used in folklore for a long time in many diseases. In this review, the study methodology adopted used Ayurvedic literature and modern scientific research-based publications, including online databases, journals and periodicals. This review provides a basis for future research work in different aspects of the field of drug research in Ayurveda [27].

**Pratima, et al (2025)** Prepared the topical formulations i.e., creams and evaluated following inclusion of fractionized ethanolic extract of *Enicostemma littorale* Blume containing flavonoids. Also, the antioxidant and anti-cancer effect of this plant extract alone and after addition in the formulation was evaluated using chemiluminescence and the stable free radical 1, 1-diphenyl 2-picrylhydrazyl (DPPH) and Dalton's lymphoma ascetics cells (DLA) cell lines assays. Formulations with plant extracts alone and the formulation containing ethanolic extract showed great antioxidant and anti-cancer activities [28].

**Shimple, et al (2025)** Conducted to search the qualitative analysis of the plant material of *Enicostemma littorale*. Qualitative phytochemical evaluation was carried out to test the presence of alkaloids, Terpenoids, flavonoids, carbohydrates, tannin, saponin, amino acid, glycoside and phenol in the methanol, petroleum ether and acetone extracts

of plant material using Soxhlet extraction methods. The present effort is targeted at the evaluation of the phytochemicals present in the plant species [29].

**Putra, et al (2023)** Recognized diabetic nephropathy (DN) as diabetic kidney disease, is a kidney malfunction caused by diabetes mellitus. A possible contributing factor to the onset of DN is hyperglycemia. Poorly regulated hyperglycemia can damage blood vessel clusters in the kidneys, leading to kidney damage. Its treatment is difficult and expensive because its causes are extremely complex and poorly understood. Extracts from medicinal plants can be an alternative treatment for DN. The bioactive content in medicinal plants inhibits the progression of DN. This work explores the renoprotective activity and possible mechanisms of various medicinal plant extracts administered to diabetic animal models. Research articles published from 2011 to 2022 were gathered from several databases including PubMed, Scopus, ProQuest, and ScienceDirect to ensure up-to-date findings. Results showed that medicinal plant extracts ameliorated the progression of DN via the reduction in oxidative stress and suppression of inflammation, advanced glycation end-product formation, cell apoptosis, and tissue injury-related protein expression [30].

**Kantha, et al (2020)** Collected the plants from Talakona forest near Tirupati to evaluate antidiabetic by ethyl acetate active fraction (EAAF) (200 mg) using animal models. Leaf materials were shade dried and coarsely powdered in order to extract the ethyl acetate active fraction, and were observed for treatment with ethyl acetate active fraction (EAAF 200 mg/kg b.wt.) which significantly normalized the blood glucose levels in STA-diabetic rats. Light microscopic studies also revealed the protective effect of EAAF on pancreatic  $\beta$ -cells and the results were comparable with the reference drug glibenclamide. The hematological parameters like erythrocyte, leukocyte, and hemoglobin were thoroughly studied [31].

**Sanmugarajah, Vinotha. (2020)** Reviewed *vellarugu* {*Enicostemma littorale* Blume (*E. littorale*)} (Gentian family) is a highly nutritious perennial medicinal plant and used as a medicine in Siddha Medical System to treat several disease conditions such as diabetes mellitus, rheumatism (Vata diseases), skin diseases (Pitta diseases), constipation, abdominal ulcers, swelling, obesity and insect poisoning. It is a rainy season herb, growing on moist, damp and shady ridges and slopes of the borders of cultivated fields and widely distributed in India, Eastern and Southern Africa, South America, and Asia. Whole plant, Leaves, Flowers, stem and Roots are mostly used for the treatment. Although there are numerous scientific studies related to multiple usage of *Vellarugu* plant, this study attempts to collect all available information and prepare a monograph about the *E. littorale* for documentation purpose. *E. littorale* has a number of anti-oxidative phytochemicals which include five alkaloids, catechins, saponins, two sterols, triterpenoids, phenolic acid, flavonoids, xanthenes and volatile oil, swetiameerin, and gentianine. Higher percentage of total ash, water soluble ash and acid insoluble ash also were found in this plant. *E. littorale* has very low toxicity and is a safe and the presence of heavy metals was below the WHO/FDA permissible limits. Numerous studies stated that *E. littorale* has the therapeutic pharmacological actions such as anti-diabetic, antioxidant, hypolipidaemic, hepatoprotective, anti-inflammatory, analgesic, anti-arthritic, anti-microbial, anti tumour, and etc. This monograph may provide and confirmed the documentary evident for multiple medicinal and therapeutic uses and pharmacological effects of the *E. littorale* [32].

**Ahamad, et al (2020)** Evaluated swertiamarin-rich fraction of *E. littorale* in controlling post prandial hyperglycemia through the inhibition of carbohydrate metabolizing enzymes in in-vitro and in-vivo studies. Standardized extract of *E. littorale* (SEL) was prepared by ultrasound assisted extraction (UAE) and its swertiamarin content was estimated by HPTLC. The content of swertiamarin was found to be  $13.62 \pm 1.46$  (%)

w/w) in SEL on dry weight basis. The effect on  $\alpha$ -amylase and  $\alpha$ -glucosidase was evaluated in-vitro. It was followed by antihyperglycemic studies in carbohydrate challenged normal and STZ-induced diabetic rats. SEL was found to inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase with IC50 values of  $12.29 \pm 0.31$  mg/ml and  $9.42 \pm 0.61$  mg/ml, respectively. In-vivo studies with normal and diabetic rats revealed that the treatment with SEL (200 mg/kg b.w.), twenty minutes prior to carbohydrate challenge produced significant ( $p < 0.01$ ) blood glucose lowering effect in both the models. The present study clearly indicates the beneficial effects of swertiamarin-rich fraction of *E. littorale* in controlling post prandial hyperglycemia [33].

**Doss, et al (2021)** Evaluated the anti-hypertrophic potential of the aqueous extract of *Enicostemma littorale* (*E. littorale*) against isoproterenol induced cardiac hypertrophic rat models (male albino Wistar rats) through biochemical investigations. Aqueous extract of *E. littorale* known for various beneficial properties was administered (100 mg/kg, 12 days, oral) to isoproterenol (ISO) induced cardiac hypertrophic rats (low ISO—60 mg/kg, 12 days and high ISO—100 mg/kg, 12 days, subcutaneous) and were compared with group that was treated with the reference drug, Losartan (10 mg/kg, administered for 12 days, oral). The anti-hypertrophic effect of *E. littorale* was evaluated by analysing the morphometric indices of the heart, ECG tracings, changes in blood biochemical parameters viz., serum glucose, serum total protein, serum albumin, lipid profile, cardiac specific enzymes (SGOT, SGPT and LDH) and histopathological examination of the heart tissue. The results fundamentally revealed that the plant extract efficiently ameliorated cardiac hypertrophy induced by ISO injected in experimental rats. The outcomes of biochemical investigations of this study highlighted the association between the hypertrophic  $\beta$ -adrenergic receptor signalling ( $\beta$ -AR) and the 5' AMP-activated protein kinase (AMPK) peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ) axis in the

metabolism of cardiac fibrosis and hypertrophy. This  $\beta$ -AR/AMPK-PGC1 $\alpha$  signalling stem can serve as a key target in ameliorating cardiac hypertrophy through focus on its principal regulators. The glycoside, swertiamarin present in this plant with the reported anti-fibrotic potential in liver can be further isolated and evaluated for its anti-hypertrophic potential to treat cardiac hypertrophy. [34]

**Wang, et al (2019)** Investigated the anti-diabetic and renoprotective effects of Cassiae Semen extract (CSE) in streptozotocin (STZ)-induced diabetic rats. Five compounds, including two anthraquinones and three naphthopyrones were simultaneously determined in CSE. Compared with diabetic control, groups treated with CSE exhibited an anti-diabetic effect, including a significant amelioration in body weight, glycemic control, oral glucose tolerance and lipid metabolism ( $P < 0.01$ ). Moreover, oxidative stress and inflammatory responses decreased after oral administration of CSE ( $P < 0.01$ ). CSE also showed protective effects on renal functions, decreasing the ratio of kidney/body weight, 24 h urine volume, 24 h urine protein, serum creatinine (Scr) and blood urea nitrogen (BUN) ( $P < 0.01$ ). Additionally, renal protective effect was also observed in histopathological examination. Immunohistochemical analysis showed that CSE downregulated the expression of RAGE [35].

**Vigneswaran, et al (2017)** Reviewed *Enicostemma littorale* Blume. is one of the perennial herb of the family Gentianaceae is cosmopolitan species occurrence in India. The bitter natural plant which is important indigenous medicine for treatments various ailments like laxative, tooth decay, obesity, curing fever, skin diseases, rheumatism, abdominal disorders, snake bite and helps to regulate blood sugar levels. *E. littorale* possesses valuable bioactive compounds including alkaloids, saponins, catechins, sterols, phenolic acids, triterpenoids, flavonoids and xanthenes. In-vitro studies and in-vivo models have provided a simple bio-scientific justification for

its various ethanopharmacological uses. The plant also contains minerals like calcium, iron, potassium, phosphate, carbonate, chloride sulphate and silica. Moreover, they also possess significant antimicrobial, anti-inflammatory, hepatoprotective hypolipidaemic and hypoglycaemic properties. Meticulous phytochemical studies and sustainable conservation of *E. littorale* could yield more reliable compounds of pharmacological significance for better healthcare [36].

**Srivastava, et al (2016)** Demonstrated potent anti-apoptotic and cyto-protective activity of *Enicostemma littorale* MeOH extract (EL MeOH ext.) against 50  $\mu$ M H<sub>2</sub>O<sub>2</sub> in isolated rat Islets. Materials and methods In this study, the whole plant methanolic extract of EL with doses 0.25-4 mg/mL each for the preincubation duration of 0.5-4 h against 50  $\mu$ M H<sub>2</sub>O<sub>2</sub> were tested for optimum protective dose and time by Trypan blue dye exclusion assay. Islet intracellular reactive oxygen species (ROS) was quantified by DCFDA staining and cell death using PS/PI & FDA/PI staining. Further, comet assay, biochemical assessment of caspase-3 and antioxidant enzyme activities along with immunoblotting of PARP-1, caspase-3, TNF- $\alpha$  activation and p-P38 MapK (stress kinase) induction was performed. Results The optimized dose of EL MeOH ext. 2 mg/mL for 2 h was used throughout the study, which significantly decreased total Intracellular ROS and cell death. Further, caspase-3 activity, PARP-1 cleavage, p-P38 MapK (stress kinase) activation and TNF- $\alpha$  levels, which had been significantly elevated, were normalized. Antioxidant enzymes like catalase, superoxide dismutase, reduced glutathione and glutathione peroxidase, along with Comet assay, demonstrated that pretreatment with EL MeOH ext. can augment antioxidant enzyme activities and protect from DNA damage. Discussion and conclusions Significant anti-apoptotic and cyto-protective effects were mediated by EL with Islets of Langerhans subjected to oxidative stress-induced cell death [37].

**Patel, et al (2013)** Attempted to unravel the molecular mechanism of action of swertiamarin, a compound isolated from EL, by comparing its molecular effects with those of aqueous EL extract in alleviating the insulin resistance in type II diabetes. We further investigated hypolipidemic and insulin sensitizing effect of swertiamarin in experimentally induced noninsulin dependent diabetes mellitus (NIDDM) in rats. Swertiamarin (50 mg/kg) and aqueous extract (15 grams dried plant equivalent extract/kg) were administered to rats orally for 40 days and tight regulation of serum glucose, insulin, and lipid profile was found in both groups. Their mode of action was by restoring G6Pase and HMG-CoA reductase activities to normal levels and restoring normal transcriptional levels of PEPCK, GK, Glut 2, PPAR- $\gamma$ , leptin, adiponectin, LPL, SREBP-1c, and Glut 4 genes. This suggests that both treatments increased insulin sensitivity and regulated carbohydrate and fat metabolism. This is the first report on the role of SM in regulating the PPAR $\gamma$ -mediated regulation of candidate genes involved in metabolism in peripheral tissues *in vivo* [38]

### Chapter 3: Aim and Objectives

#### Aim:

To assess the efficacy of *Enicostemma littorale* extract in improving insulin sensitivity and renal function in rats subjected to fructose-induced insulin resistance.

#### Objects:

- To extract the plant material
- To evaluate changes in blood glucose, insulin levels, and lipid profile
- To compare results with standard anti-diabetic drugs (e.g., metformin or glibenclamide)
- Histopathological examination of kidney tissues.

The Diabetes Mellitus is being one of five leading causes of deaths and debilitating disease in the world. One hundred and fifty million people were suffering from diabetes wide

reaching, which is almost five times more than the estimates one decade ago and it may double in the year 2030. For various reasons in recent years, the popularity of herbal medicines in diabetic control has increased. Natural plant drugs are frequently considered to be less toxic with lower side effects than synthetic ones. In spite of presence of large number of medicines in the pharmaceutical market, remedies from medicinal plants are used with success to treat and this disease.

This study will validate *Enicostemma littorale* as a dual-action herbal candidate for managing Type 2 diabetes and diabetic nephropathy, potentially paving the way for clinical trials and integrative medicine applications.

### Chapter 4: Plan of Work

#### Preliminary work

- Literature review
- Plant collection and authentication.
- Collection of plant material
- Preparation of crude extract

#### Pharmacognostical Screening

- Pharmacognostic screening of powder
- Phytochemical Screening of crude extract

#### In-vitro Pharmacological screening

- Anti oxidant activity of extract by DPPH method
- Anti- diabetic activity of extract by Fructose-induced insulin resistance model in rats

### Chapter 5: Plant Profile

#### *Enicostemma littorale*

*Enicostemma littorale* blume (*E. littorale*) a perennial herb of the family Gentianaceae is cosmopolitan in occurrence in India. The bitter 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. The plant constituents have been reported for possessing antimicrobial, antioxidant, antiulcer, anti-inflammatory, hypolipidemic, hepatoprotective and hypoglycaemic properties. This review

provides a bird's eye view about geographical distribution, physicochemical parameters,

phytoconstituents and pharmacological properties of *E. littorale*. [39]



**Figure 3: Plant of *Enicostemma littorale*.**

#### **Vernacular names:**

The ayurvedic name of *E. littorale* is Nahi, Maja-Makka booti, Vellarugu in Tamil, Vallari in Malayalam, White head in English, Chikka chiraayuta in Kanada, Mamajjakah in Sanskrit, Mamejavo in Gujarati, Nagajivha in Bengal, Chota chirayata in Hindi, Kaviyatu in Hindustani, Nela-guli in Telugu [40].

#### **Geographical distribution:**

This tropical genus is widely distributed in South America, Africa, and Asia. *E. littorale* grows in many diverse habitats from savannas, grasslands, forests to beaches, from wet to very dry and also survives in a very saline environment [41].

#### **Taxonomy:**

Kingdom:	Plantae
Subdivision:	Angiospermae
Class:	Dicotyledonae
Subclass:	Gamapetalae
Serius:	Bicarpellatae
Order:	Gentianales
Family:	Gentianaceae
Genus:	<i>Enicostemma</i>
Species:	<i>Littorale</i>

#### **Morphology of *E. littorale*:**

*E. littorale* is an erect, perennial herb, 5–30 cm tall, simple or branched at the base. Stem cylindrical, glabrous with a decurrent ridge below each leaf. Leaves are sessile sometimes narrowed into a petiole-like base, longer than the

internodes; lamina (5.0-8.0×0.3-1.0) 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 auxiliary clusters, numerous in the axils of each

pair of leaves. Flowers are white with green lines, drying yellowish, sessile or subsessile; bracts long, shorter than the calyx, lanceolate-acuminate, carinate [42].

Calyx tube 1–2 mm long; lobes usually unequal, (0.7-1.5×0.4-0.7) 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 3.5–6.0 mm long; lobes (1.5-2.0×0.7-1.0) 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 [43].

#### **Chemical constituents:**

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. The presence of minerals like iron, potassium, sodium, calcium, magnesium, silica, phosphate, chloride, sulphate and carbonate were estimated in the qualitative analysis of ash. Natarajan and Prasad reported the presence of five alkaloids, two sterols and volatile oil. Betulin, a triterpene saponin was also isolated by earlier workers [44].

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 glucosylisowertisin. The presence of catechins, saponins, steroids, saponin, triterpenoids, flavonoids and xanthenes and a new flavone C-glucoside named as Verticillside was isolated for the first time this species was reported by Jahan et al. Swertiamarin compound was isolated from *E. littorale* by using alcoholic extract. Six phenolic acids like vanillic acid, syringic acid, p-hydroxy benzoic acid, protocatechuic acid, p-coumaric acid and ferulic acid. Methanol extract of *E.*

*littorale* was found to be containing different aminoacids like 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 [45].

#### **Uses in folklore medicine:**

*E. littorale* is traditionally used in India as a stomachic, bitter tonic, carminative to reduce fever and as a tonic for appetite loss. 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. *E. littorale* has demonstrated its anti-inflammatory activity, and tumour inhibition in rats and the plant possesses a secondary compound namely swertiamarin which shows central nervous system (CNS) depressant effects in rats [46]. Nampalliwar and Godatwar observed that *E. littorale* enhances glucose-dependent insulin release [47]. The hot aqueous extract of *E. littorale* has also been used by the traditional healers for the treatment of dyspepsia and malaria.

#### **Medicinal uses:**

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