PRELIMINARY STUDY OF THE CLINICAL HYPOGLYCEMIC EFFECTS OF ENICOSTEMMA LITTORALE BLUME IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT
Type 2 diabetes mellitus (DM) is a disorder characterised by insulin resistance and a progressive. Decline in pancreatic beta-cell function associated with increasing hyperglycaemia. Type 2 diabetes mellitus (DM) is placing an increasing burden on health service delivery worldwide. Enicostemma littorale Blume, a small herb of family Gentianaceae has been used in folk medicine for the treatment of diabetes mellitus in western and southern India. Objectives: The present study was conducted to investigate the clinical hypoglycemic effects of Enicostemma littorale Blume in type 2 diabetic patients. Results: After the treatment, it is observed that there is 27.76% reduction in Fasting Blood Sugar level. Statistical analysis is carried out (paired student t-test) and ‘P’ Values is drawn which is highly significant. On statistical evaluation, it was observed that there is 36.62% reduction in Post Prandial Blood Sugar level which is highly significant. On statistical evaluation, it is observed that there is 11.52% reduction in Glycosylated hemoglobin level. Statistical analysis is carried out (paired student t-test) and ‘P’ Values is drawn which is highly significant. Conclusion: It was evident that, Enicostemma littorale produced hypoglycemic effects, thus it could be used in control and prevention of type 2 diabetes mellitus.

KEYWORDS: diabetes mellitus, Enicostemma litorale, Ayurveda.

INTRODUCTION
Type 2 diabetes mellitus (DM) is a disorder characterized by insulin resistance and a progressive. Decline in pancreatic beta-cell function associated with increasing hyperglycaemia.
Defective beta-cell function occurs early and can be detected in individuals with impaired fasting and/or post-prandial glucose levels (the so-called 'pre-diabetics'). Consequently, it has become increasingly important that physicians who treat such patients have a good knowledge and scientifically approved verity of antidiabetic drugs that are currently available or will come onto the market. The current treatment for control of DM includes diet, exercise, oral hypoglycemic drugs, and insulin therapy. However, insulin and other oral hypoglycemic drugs have characteristic profile of adverse effects. This has initiated the identification of novel drugs which might act in mechanistically distinct way compared to existing drug targets. Hence, research is focused on medicinal plants which are used in the traditional practices and development of newer drug leads with more potential and effective agents with lesser side effects than the existing hypoglycemic agents. Plants used in folk medicine to treat diabetes mellitus represent a viable alternative for the control of this disease.

Enicostemma littorale Blume, a small herb of family Gentianaceae is commonly used by rural folk’s in India. Enicostemma littorale Blume (Enicostemma hyssopifolium) commonly known as Nagajihva or Mamejava in Ayurveda, is a glabrous perennial herb growing throughout India, more frequently near the sea and tropical areas. E. littorale has been used in folk medicine for the treatment of diabetes mellitus in western and southern India. Various Ayurvedic antidiabetic formulations contain E. littorale as the only ingredient or as one of the major herbal ingredients. The plant has been reported to produce antidiabetic activity in non-insulin dependent diabetic rats. The plant contains catechins, sterols, saponins, steroids, triterpenoids, alkaloids, and volatile oil. Some important chemical constituents include betulin, a secoiridoid glycoside swertiamarin, and monoterpen alkaloids, enicoflavine and gentiocruccine. Swertiamarin was reported to be present in the members of the Gentianaceae family, E. littorale, Swertia chirata, S. japonica, and Centaurium minus.

Aims and Objectives of the study
1. To access the hypoglycemic effect of the formulation.
2. To verify the Folklore claim.
3. To provide a cost effective remedy of Diabetes.
MATERIALS AND METHODS

Plant material
Whole plant material of E. littorale was collected from Rewa, Madhya Pradesh (India) in August–September, at the end of flowering season. The plant was identified from its morphological and microscopical features as mentioned in different standard texts and floras by Dr. K.S. Karbhal in charge drug testing lab Govt. Ayurvedic Pharmacy, Raipur, Chhattisgarh (India).

Extract preparation: Whole plant material of E. littorale was powdered in grinding mill and passed through sieve no. 8. Following general principles, 2 kg coarse powder of E. littorale was added with 16 parts of potable water\(^{[10]}\) in a stainless steel vessel and the contents were soaked overnight (12 hour). The next day, Decoction was prepared by applying constant mild heat to the mixture to facilitate evaporation and intermediate stirring was carried out till the volume reduced up to one-eighth of the initial quantity. After desirable reduction of volume, the Decoction was filtered through four folded cotton cloth and collected in a separate vessel for further processing. The residue was discarded. The prepared Decoction was subjected to further heating on a gas stove maintaining the temperature between 70°C and 75°C till a semisolid consistency was obtained. Then the material was shifted into a glass tray and placed in a hot-air oven at 45°-50°C for complete drying. After complete drying, the content was grinded in a mixer grinder, collected in duly labeled air-packed glass bottle.

Inclusion Criteria
1. Newly detected diabetic cases with history of 0-5 years, also who were taking allopathic Medicine however their blood sugar was not controlled were selected.
2. Age group between 25 – 75 year
3. Fulfillments of diagnostic Criteria.

Diagnostic Criteria:
Standard criteria of National Diabetes Data group and W.H.O. for DM was adopted which are as follows: (Adopted by American Diabetic Association)\(^{[11]}\)
Symptoms of Diabetes + Random B. Glucose 200 mg/dl or more

OR

Fasting blood glucose 126 mg/dl or more.

OR

Two hours blood glucose 200 mg/dl or more (during an oral glucose tolerance test)
Exclusion Criteria
1. All patients of diabetes mellitus receiving insulin.

A detailed pro forma was prepared. History was taken and on basis of history and physical examinations the patient which was found having above complications were excluded.

Investigations: Blood sugar both fasting and Post Prandial, Urine Sugar, Total Leucocyte count, Blood Urea, Serum Creatinine, SGOT, SGPT, HbA1c (only before and after trial). All investigations were carried out in a regular interval of 15 days along with before and after treatment.

Total Duration of Treatment: 60 days.

Assessment Criteria: After completion of treatment, the results were assessed by using following criteria: FBS and PPBS level, HbA1c value. Apart from these 3 criteria other investigations are carried out only for safety of the patients. These values were recorded both before and after treatment. In order to assess clinical improvements different subjective parameters were also taken into consideration i.e., excessive urination (polyuria), turbidity of urine, tiredness, excessive sleeping, excessive sweating, excessive thirst (polydipsia) and excessive hunger (polyphagia).

Dosage form: Capsule.
Dose: 3caps thrice daily orally.
(Approx. 1.5 gm./day).

**Vehicle:** Luke warm water.

**Trial design:** single arm study (without control group)

**Ethical considerations:** Ethical clearance was obtained from the institutional ethics committee (IEC). Consent forms were signed by participants, being interested in joining the study completely voluntary.

**RESULTS**

After the treatment, it is observed that there is 27.76% reduction in Fasting Blood Sugar level. Statistical analysis is carried out (paired student t-test) and ‘P’ Values is drawn which is highly significant (table-1) On statistical evaluation, it is observed that there is 36.62% reduction in Post Prandial Blood Sugar level which is highly significant (table-2). On statistical evaluation, it is observed that there is 11.52% reduction in Glycosylated hemoglobin level. Statistical analysis is carried out (paired student t-test) and ‘P’ Values is drawn which is highly significant (table 3).

**DISCUSSION**

Obesity and insulin resistance are major causes of Type2DM. Multiple problems in diabetes lead to a cascade of complications in peripheral tissues. For controlling hyperglycemia, dyslipidemia, and insulin resistance, many synthetic drugs have been used. Also, the beneficiary effects of herbal extracts and compounds have been explained. [12] Previous
studies have demonstrated hypoglycemic effect of aqueous extract of E. littorale in alloxan-induced diabetic rats. The molecular mechanisms of action have not as yet been clearly established. However it is thought that by the action of drogue insulin sensitivity is improved and mediated via modification of post-receptor signaling in the insulin pathway. The mainstay of action of this drug can be attributed to its hepatic effects. Hepatic sensitivity to insulin is increased, thereby reducing gluconeogenesis as well as glycogenolysis, which contribute to the post-prandial plasma glucose lowering Effects. Skeletal muscle and adipocytes undergo up-regulation of the insulin-sensitive GLUT-4 and GLUT-1 transporters to the cell membranes, thereby increasing glucose uptake.

Insulin sensitivity depends on the binding of insulin to its receptor, which autophosphorylates and further leads to downstream signaling cascade. In a previous study treatment of diabetic animals with aqueous extract of E. littorale showed increased insulin receptor protein synthesis and its autophosphorylation in liver and adipose tissues, which improves insulin sensitivity in Type2DM. Phosphorylation of PI(3)K is mainly responsible for insulin stimulated glucose uptake by Glut 4, which is responsible for peripheral glucose disposition in muscle and adipose tissue. It has been reported here that aqueous extract of E. littorale improves insulin action and glucose uptake by enhancing the insulin signaling pathway in skeletal muscle.

Adipose tissue plays an important role in fat metabolism. In Type2DM, increased lipolysis and decreased lipogenesis occur in liver and adipose tissues. Obesity decreases expression of lipogenic genes like SREBP-1c, PPAR-γ, and aP2, which causes increase in hepatic lipogenesis hence leading to a fatty liver. PPAR-γ is a key transcriptional factor regulating the expression of SREBP-1c, leptin, adiponectin, and LPL. Low adiponectin and high leptin levels can cause insulin resistance in adipocytes thus leading to diabetes. It was previously evident that aqueous extract and regulate PPAR-γ mRNA levels in NA-STZ-induced diabetic rat model along with induced expression of adiponectin, LPL, and SREBP-1c suggesting it as a potent modulator of diabetes-related modification in adipocytes and thus corrects overall lipid metabolism, which can correct dyslipidemia by increasing insulin sensitivity.

The result of the current study gives strength to the hypothesis that aqueous extract of E. littorale activates PPAR-γ and its regulatory genes, which improves fat metabolism in adipose tissue. By controlling PPAR-γ, aqueous extract of E. littorale can maintain the status of small adipocytes that reduces expression of leptin and TNF-α and increases expression of
adiponectin. Increased Adiponectin secretion acts in an autocrine and paracrine manner, which improves expression of insulin receptor, its autophosphorylation, and downstream insulin signaling in liver as well as in adipose tissue. Moreover, it was worthy noted that oral administration of E.littorale extract in type 2 DM produced a significant hypoglycemic activity and favourable good health effects which may be most probably attributed to improvement and/or regeneration of pancreatic beta-cells. E.littorale acts as a hypoglycemic agent by mechanisms rather than increasing insulin levels having extra pancreatic effects acting directly on tissues as liver, muscles etc. and alters the activities of the regulatory enzymes of glycolysis, gluconeogenesis and other pathways.

CONCLUSION
The challenge of treating type 2 DM grows by the day as the number of patients increase. Therefore, a good understanding of the available treatment modalities is of great value. The results of the current study enlighten the folklore clams this is the need of the hour, a drug which is able to maintain a balance between all the players involved in the carbohydrate and fat metabolism in the peripheral tissues. This study demonstrates E.littorale efficacy in a small population of a particular Area. Further studies should include a larger population of patients, including different locations.

Abbreviations
EL: Enicostemma littorale
G-6-Pase: Glucose 6 phosphatas
GLP-1: Glucagon-like peptide-1
Glut2: Glucose transporter-2
Glut4: Glucose transporter4
HGP: Hepatic glucose production
IR: Insulin receptor
OGTT: Oral glucose tolerance te
PI(3)K: Phosphatidylinositol 3-kinases
PPAR-γ: Peroxisome proliferator-activated receptor gamma
LPL: Lipoprotein lipase 1
REFERENCES


