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Review Article

Enicostema axillare subsp. *littorale* (Blume) A.Raynal for Type 2 Diabetes mellitus: An overview

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Abstract : Introduction

Diabetic patients often consume traditional medicines, available as over-the-counter products, concurrently with prescribed conventional medicines. A study of 180 marketed Ayurvedic antidiabetic formulations showed that *Enicostema axillare* subsp. *littorale* (Blume) A.Raynal (*Mamajjakah)* is being used frequently in several formulations by Ayurvedic industry, particularly from the Western India. The present overview covers the classical and current literature on the plant for its antidiabetic activity.

Materials and methods:

The classical Ayurvedic literature, the current texts of *Dravyaguna Vidnyan*, Ayurvedic journals as well as pharmacological literature on *E. axillare* have been reviewed for its *Ayurvedic Dravyaguna* rationale and antidiabetic activity.

Results:

The earliest description of the plant *E. littorale* has been found in *Shodhal Nighantu (12th Century)* with its various synonyms and its use as an antipyretic and anthelminthic drug. Medicinal properties of the plant in classical and other texts reveal that it can best be described as *laghu* (light), *ruksha* (dry), of tikta *rasa* (pungent taste), *ushna veerya* (hot potency) and *katu vipak* (after-effects like pungent taste). It ameliorates *pitta* and *kapha doshas*. Its main site of action is *medodhatu* (adipose tissue) having *pramehaghna* (antidiabetic) properties. The phytochemical studies show major molecules that have shown antidiabetic properties are swertiamarin, apigenin and isovitexin. Several *in vitro* studies have demonstrated its antioxidant and anti-inflammatory activities; while *in vivo* studies have shown antidiabetic, antihyperlipidemic, antihypertensive, antiobesity, nephroprotective, hepatoprotective as well as antioxidant and anti-inflammatory activities. Several clinical studies have reported safety and antidiabetic activity in diabetic as well as prediabetics patients. Besides these, the plant has also shown nephroprotective, genoprotective activities as well as insulin sensitization.

Conclusions:

Wide use of *E. axillare* in diabetes mellitus suggests a need for thorough survey of its Ayurvedic pharmaco-epidemiology and drug utilization. The emergent data would facilitate Reverse Pharmacological study of the plant in diabetic patients. There is a potential for developing a safe and validated phytopharmaceutical antidiabetic drug.

Key words: Diabetes, Ayurvedic Pharmacoepidemiology, *Enicostemma axillare* subsp. littorale, *Mamajjakah ,* Reverse Pharmacology

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Introduction

India is called "the diabetic capital of the world" and there is an immense economic burden on the country due to the disease. Currently, 62 million people are diabetic and by 2030, the number is projected to be 100 million.[1] The complex nature of the disease demands prolonged drug

therapy that compels diabetic patients to seek alternative management like traditional herbal remedies. Prevalence of using traditional or complementary medicine across different countries is 15 to 75%, while it is around 68% in India.[2-5]

Pluralistic health care is quite unique to India; this offers patients an opportunity to consume traditional medicines concurrently with conventional medicines. Very large population of the country utilizes traditional medicines, which are predominantly plant based.[6] People have faith in the safety of Ayurvedic herbal medicines, and often accept the advice of pharmacist. Diversity of traditional formulations available as over-the-counter (OTC) supplements or herbal medicines is overwhelming. However, many products are not supported by clinical evidence data on the safety and efficacy.[7-8]

The study of marketed antidiabetic Ayurvedic formulations revealed that several Ayurvedic formulations are available as OTC to the diabetic patients.[9] *E. axillare* subsp. *littorale* has been used frequently in the antidiabetic formulations by Ayurvedic drug manufacturers from the western India. Besides being prescribed by Ayurvedic physicians, it is also available as an ingredient in several OTC drugs. The plant is investigated extensively *in-vitro* and *in-vivo* studies from the late 1960s. Vaidya ADB and his team started clinical screening of antidiabetic plants and formulations for their activity since 1970.[10] Trails were followed up from the literature of ethnobotany, interviews of *vaidyas*, classical texts and field surveys. During the next decade placebo-controlled studies were conducted in volunteers and diabetic patients for antidiabetic effects.[10]

This overview covers classical and current literature on the use of the plant, its *Ayurvedic Dravyaguna* (pharmacological) properties and biological plausibility based on preclinical and clinical data. Such an overview would facilitate development of a safe and validated phytopharmaceutical antidiabetic drug from *E. axillare* subsp. *littorale*.

Materials and Methods

Secondary survey of the literature sources for the overview included the following:

1) Classical Ayurvedic texts, 2) Authentic texts/ monographs approved by the Ministry of AYUSH, Government of India, 3) Current and earlier textbooks on *Dravyaguna Vidnyan*, 4) Ayurvedic journals, 5) Health periodicals, 6) *Vaidyas'* notes, 7) Ph D/MD theses, 8) Published citations, 9) Pubmed, 10) Cochrane library, and 11) Google search and Google scholar, etc.

These methods involved tabulations and listing of indications, precautions, dosage, formulations, phytoactives, research models with relevant references.

Results

1. Classical literature

- **Ayurvedic Literature**

Mamajjakah (*Enicostemma axillare* has not been mentioned in the *Vedic* texts. There is no description in Brihattrayi and Laghuttrayi either. The plant has first been described in *Shodhal Nighantu* in the 12th century for its use as an anti-helminthic and *in ksharkarma*.[11] The description of various application of the plant as described in the Ayurvedic literature is presented in Table 1.[12-20]

- ***Ayurvedic Dravyagunas***

The literature search suggests that the plant has been used since 12th century, however, its use is yet not widespread in India. The plant is described as having properties of laghu (light), *ruksha* (dry), of tikta *rasa* (pungent taste), *ushna veerya* (hot potency) and *katu vipak* (after-effects like pungent taste). It ameliorates *pitta* and *kapha doshas*. Its prominent use is in fever and worm infestation. Table 2 describes Ayurvedic properties of the plant as reviewed from the literature.[21]

- **Human use**

Aryavaidya Mayaram Sundarji in his notes (H" 1907 A.D.) mentions the human use of *Mamajjakah* for fever with its dosage.[22] He mentioned that in the coastal area of Surat

(Gujarat), the plant is known as '*Kadvi Nai'* (with equivalence of *Mamejava)*. October, 1940 issue of "*Vaidya Kalpataru*" has a letter from *Vaidya* Amritlal Padhiar mentioning '*Kadvi Nai'* and its clinical uses in fever, healing of maggot-infested wounds and for abdominal colic pain.[23]

It is difficult to precisely trace the date and origin of the use of the plant in diabetes mellitus. Ayurvedic physicians have been using the plant singly and as an ingredient of various formulations since decades. At Gujarat Ayurveda University and at Akhandananda Ayurveda Hospital (Ahmedabad), *Mamejava ghanavati* has been used extensively. Dr. Harindra Dave at the latter centre has a large experience of its use in diabetes and diabetic retinopathy.[24]

2. Phytochemistry of *E. axillare*

First reports of its phytochemical analysis appeared in 1966 by Raj and Thakkar[25] and Desai et al.[27] Detailed study of physico-phytochemical evaluation of aqueous extract of *E. axillare* was reported by Tanna *et al*.[26] The class of phytoconstituents are shown in Table 3 with names of compounds and the type of extracts. Among the listed compounds, swertiamarin - an iridoid glycoside, apigenin- a flavonol, and swertisin – a flavone can be used as marker compounds. The chemical structures of the phyto-molecules are shown in Figure 1.

3. Pharmacological Literature

- ***In-vitro* Activity**

Alcoholic extracts from *E. axillare* subsp. *littorale* have been studied in several *in-vitro* models for their antidiabetic, antioxidant and anti-inflammatory activities. Alcoholic extracts have shown anti-inflammatory and antioxidant activities. Stem cell lines (PANC-1& NIH3T3) have been studied for glucose induced insulin release. NIH3T3 cells have shown differentiating property into endocrine cells after treating with methanol extract of Swerticin (15mcg/ ml for 8 days) and glucose induced insulin release. Table 4 describes the activity of investigational extracts and the models used.

- **Experimental pharmacology**

Diverse animal models for diabetes, inflammation, oxidant damage, dyslipidaemia etc. have been investigated for antidiabetic activity and diabetes related complications. Aqueous as well as alcoholic extracts have been investigated for antidiabetic activity. *E. axillare* has shown significant antidiabetic, anti-dyslipidemic, antioxidant, nephroprotective, antihypertensive, antiobesity activities. Vishvakarma *et al.* reported that aqueous, n-butanol and ethyl acetate extracts of the plant significantly decreased glucose, lipids and creatinine in STZ induced diabetic rats.[42] Table 5 shows various experimental studies regarding antidiabetic targets.[41-53] Alpha -amylase inhibitory activity of erythrocentaurin *and* α-glycosidase inhibitory activities of the plant have also reported.[54, 55]

- **Clinical Studies**

E. axillare has been studied clinically by several groups. A book published by Dr Baghel and Girish KJ (now available online) gives the information regarding MD and Ph D theses of Ayurveda on *Mamajjakah* (*E. axillare*).[56, 57] It is noted that the work on this plant was started in 1965 at Gujarat Ayurved University, *Davyaguna* Department by Dr Jyotishi who had studied *Madhumeha par mamajjak prayog* (*E. axillare* for diabetes).[56]

Selected antidiabetic plants and formulations (recommended and used by expert *Vaidyas*) were studied in diabetic patients over a long period at Podar Ayurvedic Hospital in close collaboration with CIBA Research Centre.[10] Scientists of several institutes have worked collectively and extensively in a nation-wide CSIR NMITLI (Council of Scientific and Industrial Research-New Millennium Indian Technology Leadership Initiative) on Diabetes project on *Mamejava ghanavati* (prepared as per Ayurvedic methodology) following the Reverse Pharmacology approach.[58,59] Phase I, II and III clinical trials have shown safety and antidiabetic activity.[60] Genoprotective activity of *Mamejava Ghanavati* in diabetic patients has also been reported by Shet *et al*.[61] Drug interaction study of *Mamejava ghanavati* in healthy volunteers showed that 'co-administration of (*Mamejava*) ghanavati with metformin at a single dose did not show

any significant difference in the mean AUC of metformin (P = 0.645)' as reported in the study.[62] During the research work of this project (2007-2007), a new discipline of Ayurvedic Pharmacoepidemiology was proposed by Dr Rama Vaidya.[63] Table 6 summarises the clinical Studies on the plant and the formulations, dosage and results by these groups.

Conclusion

Ayurvedic literature shows that *E. axillare* subsp. *littorale* has been used for several disorders. It has been used for fever and worm infestation that may be pertinent to *tikta rasa and deepan-pachan karma.* Medicinal properties of the plant provide evidences for its *shothhar* (anti-inflammatory), *krimighna* (anthelminthic) and *raktaprasadan* (blood purifier) activities. It is supported by the phytoconstituents of the plant that are known for their anti-inflammatory and antioxidant activities. Formulations containing *mamajjakah* are most commonly marketed for diabetes. There have been several clinical studies that substantiate this activity of *E. axillare* subsp. *littorale* extracts. *E. axillare* subsp. *littorale (mamajjakah)* has emerged as a potential antidiabetic plant based on evidences provided by studies using Ayurvedic pharmacological approach and application of Reverse Pharmacology. Further studies on validation of products developed based solely on this plant or in combination with other herbs shall provide scientific support to propagate this unique Ayurvedic knowledge. To conserve the plant, collective efforts should also be made towards its mass cultivation through traditional, clonal propagation and tissue culture techniques.

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Table 1 Various applications of the plant as reported in Ayurvedic texts, journals, etc.

Nighantu/ Ayurvedic texts	Description	Ref. #
Shodhal Nighantu	• Anthelminthic	11
Shaligram Nighantu	• Bitter taste of leaves • Use in *ksharkarma* and as antiparasitic	12
Bhavprakash Nighantu	• Antipyretic and anthelminthic	13
Bheshaj Samhita, Health Ministry of Gujarat	• Preparation of *Mamajjak Ghana* • *Vati* as antipyretic (*Vishamajwara*)	14
Aushadhi Sangraha	• Appetizer, mild laxative, • Facilitates the metabolism.	15
Vanoushadhi Chandrodaya	• Bitter and pungent taste • Anthelminthic, antipyretic and *vata* disorders.	16
Vanoushadhi Gunadarsh	• Bitter taste • Antipyretic and antihelminthic	17
Nighantu Adarsh	• Juice of leaves with *Piper nigrum* for fever • Powder for malarial fever with buttermilk. • Anthelminthic and antidiarrheal	18
Vanaspati Varnan	• Detailed description of morphology • Recommended in *vata*-vitiated disorders. • Anthelminthic and antipyretic	19
The Wealth of India	• Whole plant powder with honey as a blood purifier • For dropsy, rheumatism, hernia, swelling, itches, filariasis, insect bite and tape worm infestation	20

Table 2 Ayurvedic properties of the plant *Mamejava*[21]

Name	*Nagajivha E. axillare* subsp. *littorale*
Gana	*Haritakyadi*
Synonyms	*Nahi* , *Nagdamani*, *Mamejava* , *Tikshnapatra* , *Tiktapatra*
Properties	*Laghu* (Light), *Ruksha* (Dry),
Rasa/Taste	*Tikta* (Bitter),
Veerya/ Potential	*Ushna* (Hot potency)
Vipak /After digestion effects	*Katu* (Pungent after-effects)
Doshaghnata	*Pittakaphaghna* (Pacifying *pitta* and *kapha*),
karma	*Deepan* (Appetizer), *pachana* (Digestive),*sara* (Laxative), *balya* (Strength giving), *shothhar* (Anti-inflammatory), *krimighna* (Anthelminthic), *Raktaprasadan* (Blood purifier)
Rogaghnata	*Madhumeha*(Diabetes), *kandu*(Itching), *jvara* (Fever), *vishamajvara*(Intermittent fever), *vibandha* (Constipation), *Yakrutshopha* (Hepatitis), *kushth* (Skin diseases), *Agnimandya* (Digestive impairment)
Parts used	*Panchanga* (Whole plant), *patra* (Leaves)
Dosage	Churna (Powder), 1-g daily
Formulations	*Mamejava Ghana vati*

Table 3 Chemical constituents of *E. axillare*

Compound Class	Compound Name	Extracts	Reference
Triterpene	Betulin	Chloroform extract	Raj and Thakkar 1966[25]
Seco-iridoid glycoside	Swertiamarin	Aq. Extract Aq Alc extract Alc extract	Desai/ Govindachari 1966 [27]
Monoterpene Alkaloids	Enicoflavin, Gentiocrucine	Chloroform/ alcohol extract	Ghosal 1974[28] Chaudhari 1975[29]
Phenolic Acids	Vanillic acid, Syringic acid, Protocatechuic acid, Ferulic acid, P. coumaric acid	Aq-Alc. extract	Daniel & Sabnis 1978[30]
Flavonoids & Flavone glycoside	Apigenin, genkwanin Isovitexin, Swertisin, Saponarin, Swertisin-5-0-glucoside, Isowertis-5-0-glucoside	Aq. extract. Alc. extract Aq. Alc. extract	Ghosal & Jaiswal 1980[31]
Amino acid	L- glutamic acid, alanine Serine, aspartic acid, l-proline, l-tyrosine, phenyl alanine, methionine isoleucine, l-arginine, DOPA, glycine, GABA	MeOH extract Aq. MeOH extract	Retnam 1988[32] Satishkumar *et al.*, 2010[33]
flavone	• Verticilliside • 5,7,4'-Trihydroxyflavone8-C-beta-D-lucopyranoside • isoorientin 3'-O-methyl ether	Ethyl acetate extract of soluble fraction	Jahan *et al.*, 2009[34]
Minerals	Iron, potassium, sodium, calcium, magnesium, silica, phosphate, chloride, sulphate and carbonate	Ash	Selvum *et al.*, 2018[35]

Aq : Aqueous, Alc : Alcoholic,

Table 4 *In-vitro* studies on *E. axillare* in diverse models for diabetes

Model	Type of extract	Result	Activity	Reference
RBC membrane	Alcoholic extract	↓ Lipid peroxidase ↓Acid phosphatase	Anti-inflammatory	Sadique *et al.*, 1987 [36]
Nine diff methods	Chloroform petroleum ether Ethyl acetate and methanol extracts	↓paw-edema Scavenging of free radicals ↓Lipid peroxidation	Antioxidant activity	Vaijanathappa J *et al.*, 2008[37]
Stem cell line PANC-1& NIH3T3	SGL-1 isolated from MEOH extract, 15ug/ml	Glucose responsive insulin release.	Increase in islet cell mass	Gupta S *et al.*, 2010[38]
NIH3T3 cells	Methanol extract Swerticin; 15mcg/ ml for 8 days	Differentiating NIH3T3 into endocrine cells. Glucose induced insulin release	Rapid induction for islet differentiation From NIH3T3	Dadheech *et al.*, 2013[39]
Isolated rat islets	Methanolic extract / 0.25-4 mg/ml	Caspase3 activity PARP-1 cleavage, p-P38 MapK, & TNF-α normalization	Anti apoptotic, cytoprotective and DNA protection	Srivastawa *et al.*, 2016[40]

↓ Decreased;

Table 5 Experimental studies on *E. axillare* in diabetes mellitus.

Model	Drug/dose	Result	Activity	Reference
Normoglycemic, hyperglycaemic and alloxan induced diabetic rats	Whole plant aqueous extract 30 days	↓ blood glucose, ↓ HbA1C ↓ glucose-6-phosphatase activity in liver.	Hypoglycaemic	Vijayvargia R 2000 [41]
STZ rats	Aqueous extract (0.5, 1, 2 g/kg Ethyl acetate (0.5 g/kg) n- butanol (0.5 g/kg)	Aq, n-butanol and ethyl acetate extracts significantly decrease glucose, lipids and Creatinine	Antidiabetic, antidyslipidemic & ↓Creatinine, SGOT/PT	Vishvakarma *et al.*, 2003 [42]
Alloxan induced diabetic rats	Methanolic extract 2.5 mg/kg/w for 20 days	↓ Blood glucose ↓Glutathione ↓Lipid peroxide ↓Erythrocyte catalase activity	Antidiabetic and antioxidant, antiobesity	Maroo *et al.*, 2003 [43]
Hepatoma induced hyperlipidaemic Wistar rats	Crude powder 1 g /kg for 15 days	↓Lipids ↓γ GT ↓Lipid peroxidation	Antidyslipidemic Antioxidant	Gopal *et al.*, 2004 [44]
Alloxan induced diabetic rats	Whole plant aqueous extract 45 days 2 g/kg	↑hexokinase, ↓ glucose 6-phosphatase & fructose 1,6-bisphosphatase ↓ TBRAS, ↓lipid peroxides in brain ↑ in heart ↑SOD & catalase	Antioxidant, glucose utilization	Srinivasan *et al.*, 2005 [45]
Hyperlipidaemic rats/HFD	Swertiamarin, 50 mg/kg	↓ hyperlipidemia ↓Lipid peroxidation	Antidyslipidemic	Vaidya H *et al.*, 2009 [46]
Diabetic neuropathy in male Charles foster rats	2.5 mg/kg for 45 days	Lipid peroxidation status and anti-oxidant enzymes $Na\text{-}K^+$ ATPase activity	Nerve function and oxidative stress relief	Bhatt *et al.*, 2009 [47]
STZ DM rats with nephropathy	Aqueous extract 1 g/kg and swertiamarin 50 mg/kg daily for 3 weeks	↓ Blood urea, ↓S creatinine ↑Glomerular function	Nephroprotective	Sonavne *et al.*, 2010 [48]
STZ DM rats	Hot& cold aqueous extracts 0.5,1,2 g/kg for 3 weeks	↓ Blood glucose ↓ dyslipidemia	Antidiabetic Antidyslipidemic	Vishwakarma *et al.*, 2010 [49]
Gentamicin induced nephrotoxicity in rats	Methanolic extract 2.5 mg/kg	↑Antioxidant defence system of mitochondria	Antioxidant	Bhatt *et al.*, 2011 [50]
NIDDM rat model by intraperitoneal injection of nicotinamide dissolved in normal saline	Swertiamarin (50 mg/kg) 40 days	Restoring G6Pase and HMG-CoA reductase Normalization of PEPCK, GK, Glut 2, PPAR-γ, leptin, adiponectin, LPL, SREBP-1c, and Glut 4 genes.	Molecular mechanism, Regulate carbohydrate/ fat metabolism.	Patel *et al.*, 2013 [51]
High fat diet induced obese rats	Aqueous and ethanol extracts	↓ Weight gain	Antiobesity activity	Garg *et al.*, 2014 [52]
Adrenaline induced hypertensive rats	70% ethanolic extract 0.5 mg/kg i.p for 5 consecutive days.	↓ blood glucose, ↓serum lipids ↓serum creatine phosphokinase, ↓LDH	Antihypertensive	Chikkamath *et al.*, 2017 [53]

↓ Decreased; ↑ Increased;

Table 6 Clinical Studies on the plant and the formulations, dosage and results.

Population	Study design	Drug/dose/duration	Result	Reference
T2DM n=8	Open labelled Placebo controlled	*Mamajjakah* powder 5 g twice/day	Antidiabetic	Vaidya ADB *et al.*, 1989 [10]
Newly diagnosed T2DM n= 20	Open labelled	Aqueous extract 5 gm twice for 2 months	Antidiabetic Antioxidant	Vihas & Vasu *et al.*, 2003 [64]
T2DM n=84	Open labelled only OHA & OHA+ Insulin	*Ghana vati* for 9 months (4 pills per day)	Antidiabetic, Insulin sensitizer, Nephroprotective	Upadhyay *et al.*, 2004 [65]
T2DM n=63	Open labelled, multicentric nonrandomized	Treatment with aqueous extract of *E. littorale* pills for 9 months	Antidiabetic, antidyslipidemic and ↓ DNA damage	Mansuri *et al.*, 2009 [66]
T2DM n=10	Open labelled	2 g daily for 21 days	Antidiabetic	Nampalliwar et al., 2011 [67]
T2 DM n= 30	Open labelled	*Ghanavati* 500 mg thrice a day for 2 months	Antidiabetic Genoprotective by ↓SCE	Sheth *et al.*, 2011 [61]
T2DM n=60	Single blind placebo controlled 3 groups	1. *Shaman (ghanavati)* 2. *Shodhan(virechan) + ghanavati* 3. *Godanti bhasma* as placebo	Better relief in *Shodhan + Ghana vati* than only *ghanavati*	Shukla *et al.*, 2013[68]
T2DM n=84	Randomised clinical study : 3 groups	1. Aqueous extract capsule 500mg/twice a day 3 months 2. Cap *shilajit* (500mg twice/day 3. OHA as per GCP	Antidiabetic & *rasayana*	Kumar *et al.*, 2014 [69]
Healthy volunteers n=12	Randomised crossover controlled with Metformin 500 mg simultaneous consumption	*Ghanavati* 750 g single dose	No significant change in metformin bioavailability	Puranik *et al.*, 2014 [62]
T2DM n=20	Open labelled	3 (500 mg each) capsules thrice per day for 60 days	Antidiabetic	Shukla *et al.*, 2015[70]
T2DM (obese) n= 20	Metformin (500 BD) controlled	5 g powder BID 12 weeks	Antidiabetic	Surse *et al.*, 2017 [71]
Metabolic syndrome n=30	Randomised placebo controlled	Aqueous extract for 3 months	Antioxidant	Vaibhav *et al.*, 2017[72]
T2DM n=162	Prospective, open-label, multi-centre, single-arm study	One gram (two tablets of 500 mg each) twice daily 84 days.	Safety shown Antidiabetic	Shubhashree MN *et al.*, 2019[73]

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