



Title: Understanding the pharmacokinetics of *mamajjaka* (*enicostemma littorale* blume) as a dietary supplement in diabetes mellitus.

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ABSTRACT:

Enicostemma littorale Blume, also known as *Mamajjaka* in Sanskrit, Indian gentian in English and “*Kadavinay*” in local language, is a perennial herb of Gentianaceae family. The plant parts like leaves and roots are used since ages in various parts of India for treating diabetes. It is widely used in Solapur and Osmanabad districts of Maharashtra, in the form of “leaf pickle” as a dietary supplement in diabetic patient. *Acharya Priyavat Sharma* has described it as useful in *madhumeha*. *Mamajjaka* has a predominance of *Tikta rasa*, *Ushna virya*, *Katu vipaka*, *Laghu-Ruksha guna* and *Vayu-Aakash mahabhuta*. It's an easily available and economically important herb. Different constituents of *Mamajjaka*, like Swertiamarin, Flavonoids, Saponins, triterpenoids, alkaloids, catechins, sterols, phenolic acids and xanthenes, have been reported for possessing hypoglycemic properties. In-vivo, anti-hyperglycemic effect of *Mamajjaka* has been established, through enhancing glucose-induced insulin release, reducing the glycosylated

hemoglobin and by inhibiting the action of glucose-6-phosphate in liver. As, all previous studies have established the significant potentials of *Mamajjaka* both in Type-1 and Type-2 diabetes, in this study we have reviewed the pharmacokinetics of *Mamajjaka*, keeping in mind the scientific basis of traditional use of *Mamajjaka* mainly as diet in diabetes. We have established the role of panchabhautic constitution of *Mamajjaka* as a dietary supplement for the diabetic patients. We have concluded that *Mamajjaka*, being cost-effective and easily available medicinal herb possessing hypoglycemic properties, can be used as an excellent vegetable in diabetic patients as a dietary supplement.

Keywords:

***Enicostemma littorale*, Mamajjaka, Ayurveda, Anti-diabetic.**

Introduction:

Diabetes is a serious, chronic, complex disorder associated with metabolic disturbances and hyperglycemia.

Management of diabetes without any side effect is still a challenge to all clinical practitioners. Current scenario of diabetes says that there were 72 million cases of diabetes in India in 2017. Also, according to International diabetic federation, 425 million people have diabetes in all over world and 82 million in South-East Asia region^[1].

There are plenty of drugs available as an oral hypoglycemic agent to lower blood glucose level in diabetics. However, most of them are expensive and unpalatable and also with many side effects. Therefore, finding of more preventive strategies and treatments especially as dietary supplement is vital. One of such herbal plants is *Enicostemma littorale* Blume. i.e. *Mamajjaka*, which can be used as a dietary supplement.

In his *Priya-Nighantu*, Acharya Priyavata Sharma has described *Mamajjaka* as a useful herb in *Madhumeha*^[2]. This plant is found to be distributed in grasslands, forests to beaches, from wet to very dry and also survives in a very saline environment, throughout India. Medicinal compounds derived from *Mamajjaka*, are considered to be very effective, since these are eco-friendly, palatable, possessing long shelf life and free from side effects^[3].

***Madhumeha* –**

It is mentioned in *Bruhatrayis*. In the *samprapti* of *Madhumeha*, Acharya Sushruta has described that *prameha* is not treated at a right time i.e. *Kalen apratikarinah*, then it is converted into *Madhumeha* and said to be *Asadhya* i.e. incurable.^[4]

According to Acharya Charaka, in the *samprapti* of *Madhumeha*, increased *Kledadi dushya's* get forcefully pulled by

dushit vata dosha into the *Basti* causing increase in the quantity along with the turbidity of urine, which can be labeled as *Prabhuta aavila mutrata*.^[5]

Diabetes –

Normally ingested food is converted into glucose by the liver and glucose is released in the blood stream. At the same time pancreatic beta cells get triggered for the insulin release. This released insulin, then stimulates the insulin receptors placed on the surface of cells, to facilitate the entry of the glucose into the cells. Thus blood glucose level gets maintained and body cells get energy from glucose.

Type 1 diabetes: In this, pancreatic beta cells are unable to produce sufficient insulin. Due to which insulin receptor does not get stimulation for glucose uptake by cells and thus glucose remains in the blood stream.

Type 2 diabetes: In this, pancreatic beta cells produce insulin properly, but there is a condition of alterations in insulin receptor which lead to insulin resistance. Due to insulin resistance blood glucose cannot move into the cells and thus glucose remains in the blood stream. Here there may be the condition of hyperinsulinemia also.

In this way, in both type of diabetes blood glucose level get increased.^[6]

Nutritive value of *Mamajjaka* –

Table– 1: Nutritive value per 100gm of fresh leaves of *Mamajjaka* (*E. littorale*) (According to report of Indian Council of Medical Research)^[7]

Components	Amount
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Energy (Kcal)	140
Protein (gm)	7
Fat (gm)	0.7
Carbohydrate (gm)	26.5
Fiber (gm)	4.2
Minerals (gm)	8.4
Iron (mg)	49.9
Calcium (gm)	1.641
Phosphorous (gm)	81

Phytoconstituents –

- 5 alkaloids, 2 sterols and volatile oil^[8]
- A triterpene saponin – betulin^[9]
- Monoterpene alkaloids – enicoflavin, gentiocrucine and 7 different flavonoids isolated from alcoholic extract. And structures were identified as apigenin, genkwanin, isovitexin, swertisin, saponarin, 5-o glucosylswertisin.^[10]
- Saponins, catechins, steroids, saponin, triterpenoids, flavonoids and xanthenes, a new flavones c-glucoside named as Verticillside^[11]
- Swertiamarin^[12]
- 6 phenolic acids – vanillic acid, syringic acid, p-hydroxy benzoic acid, protocatechuic acid, p-coumaric acid and ferulic acid^[13]
- Different amino acids – 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.^[14]

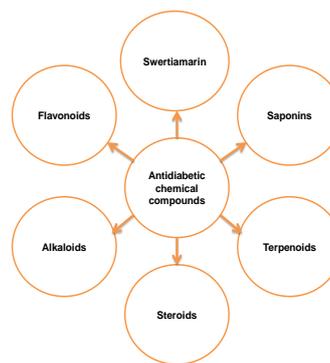


Fig. 1 Anti-diabetic chemical compounds present in *Enicostemma littorale* Blume. (*Mamajjaka*)



Fig. 2 *Mamajjaka* (*Enicostemma littorale* Blume.)^[15]

Previous workdone:

1. Jyoti M [2000], Murali B. [2002] and others found that a single dose of aqueous extract of *Mamajjaka* (15g dry plant equivalent extract /kg) had shown significant increase in serum insulin levels in alloxan induced diabetic rats at 8 hr. further insulinotropic action of this extract also investigated using rat pancreatic islets and it reveals that plant extract has potential to enhance glucose induced release at 11.1mM glucose from and was partially able to reverse the effect of diazoxide. Incubation with Ca²⁺ chelator and Ca²⁺ channel blocker (nimodipine) did not affect the

- glucose-induced insulin release augmented by the extract. Thus above results have suggested the glucose lowering effect of aqueous extract of *Mamajjaka*.^[19, 3]
2. In diabetes, hyperglycemia generates more reactive oxygen species (ROS). This increased ROS production and compromised anti-oxidant defense system leads to a decrease in glutathione (GSH) levels, increase LPO and change in CAT activity. GSH is an important factor in detoxification and antioxidant systems. GSH offers protection against oxygen derived free radicals and cellular lethality. An increase in GSH level in extract treated diabetic rats might be due to less production of ROS.
 3. Jyoti Maroo and others [2003] found that methanol extract of *Mamajjaka* decreases the glycation of Hb and liver glucose-6-phosphatase activity in alloxan induced diabetic rats. She also found increase in GSH levels; decrease in erythrocyte CAT activity and decrease in erythrocyte LPO levels in extract treated diabetic rats.^[20]
 4. Jyoti M. and others [2003] found that administration of aqueous extract of *Mamajjaka* for 45 days showed reduction in blood glucose levels.^[21]
 5. Maroo J. and others [2002] found that *Mamajjaka* potentiate the glucose induced insulin release from pancreatic beta cells and cause a decrease in blood glucose levels of extract treated diabetic rats.^[22]
 6. Maroo J. and others [2003] established that *Mamajjaka* is a potent antidiabetic agent without any toxic effect at this particular dose (1.5g dry plant equivalent extract/100gm body wt.) in alloxan induced diabetic rats. They also found the significant decrease in glycosylated haemoglobin, liver glucose-6-phosphatase activity and significant increase in serum insulin level of diabetic rats.^[23]
 7. Vishwakarma Santosh L. and others [2003] found the dose dependent effect of hot and cold aqueous extract of *Mamajjaka* (0.5, 1 and 2gm/kg for 3 weeks) on streptozotocin induced type 1 diabetic rats. It also possesses potential of antidiabetic activity and improves lipid profile at a small dose of 0.5g/kg. He also found that treatment of diabetic rats with hot aqueous extract reduced the food, water intake and glucose and AUC glucose levels and decreased the serum glucose, serum cholesterol and triglyceride levels. Swertiamarin was found to be a major component in hot extract of *Mamajjaka* while it was absent in cold extract.^[24]
 8. Upadhyaya and others [2004] found that, *Mamajjaka* 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.^[25]
 9. Prince PSM and others [2005] found that administration of aqueous extract of *Mamajjaka* for 45 days significantly decreases the blood glucose, TBARS (Thiobarbutyric acid), SOD (Superoxide dismutase), CAT (Catalase) and GP_x (Glucose peroxidase) in alloxan induced diabetic rats. When the effectiveness of *Mamajjaka* extract was compared with standard drug insulin, then it was observed that administration of



Mamajjaka extract at the dose of 2gm/kg was more effective than insulin at the dose of 6 units/kg. Hence it can be tried in clinical purpose to overcome these complications.^[26]

10. Jaishree Vaijanathappa and others [2008] found that aqueous extract of *Enicostemma axillare* prevented the blood glucose level as well as insulin level in rat model. It produces an increase in insulin sensitivity, normalizes dyslipidaemia and provides nephroprotection in diabetic rats.^[27]
11. Gite and others [2010] concluded that the leaf of *Mamajjaka* possesses hypoglycemic, anti-oxidant, hepatoprotective and hepatomodulatory properties and helps in reducing obesity^[28].
12. The multi-potent differentiation property of stem cells opens up new arena for the treatment of the diabetic patients. Many chemical and biochemical compounds make stem cells get differentiate into insulin producing cells.
13. Sarita Gupta and others [2010] in their study highlighted the islet neogenic property of the plant *Mamajjaka*. An active herbal compound SGL-1 (Sodium glucose transporter) was isolated and purified from extract of *Mamajjaka* and used to differentiate two model stem cell lines PANC-1 and NIH3T3 which showed tremendous islet neogenic potential and significant islet yield compared to control serum free medium. Morphological, molecular and immunological characterization of newly generated islet like cellular aggregates proved them differentiated and positive for islet hormones. Functional characterization of islet cellular

aggregates (ICA's) confirmed significant glucose responsive insulin release. This preliminary data offer exiting possibility of alternate source to increase islet mass which can be used for diabetic treatment.^[29]

14. Shukla Amarnath and others [2013] concluded that *Mamajjaka* extract for 45 days significantly reduced hyperglycemia in type 2 diabetes mellitus.^[30]
15. Insulin resistance is responsible for the development of hyperglycemia in NIDDM (non insulin dependent diabetes mellitus) patients. Gohil T. A. and others [2008] found that administration of aqueous extract of *Mamajjaka* for 15 days prevented hyperglycemia and hyperinsulinemia induced by a diet high in fructose.^[31]
16. Gopal R. and others [2004] found that, the aerial part of the *Mamajjaka* reduces the serum cholesterol level in hepatoma bearing rats. This activity is through a component of plant which enhances cholesterol acyl transferases by esterification of free cholesterol in the HDL (High density lipoprotein).^[32]
17. Vihas T. Vasu and others [2005] found the hypolipidaemic and antioxidant effect of aqueous extract of *Mamajjaka* at a dose of 1.5g/100g body wt/day, to rats along with hypercholesterolaemic diet. It also showed a decrease in activities of erythrocyte catalase, superoxide dismutase and lipid peroxidation levels, with an increase in reduced glutathione levels compared to untreated rats. Also there were decrease in kidney and liver cholesterol level.^[33]



18. Hitesh Vaidya and others [2009] demonstrated new property of Swertiamarin as a potent lipid lowering agent and comparable to atorvastatin and it may contribute to its cardioprotective and antiatherosclerotic role. Swertiamarin and atorvastatin when orally fed also lowered the total serum cholesterol and triglycerides.^[34]
19. Jaishree Vaijanathappa and others [2008] also found the anti-oxidant and hepatoprotective properties of Swertiamarin isolated from *Enicostemma axillare*.^[27]
20. Gupta R. S. and others [2007] found the administration of ethanolic extract of *Mamajjaka* exhibited the significant hepatomodulation against oxidative stress in rats through anti-oxidant potential and free radical scavenging activities along with reduction of fat metabolism.^[35]
21. Flavonoids are polyphenolic compounds which show an anti-oxidant effect by quenching free radicals. This might be the reason for the decrease in the erythrocyte CAT activity and LPO in extract treated diabetic rats.
22. Natarajan [1972], Ghosal [1980] and others found that extract treatment of diabetic rats decreases blood glucose levels, thereby decreasing glucose auto-oxidation and free radical generation, which in turn decreases lipid peroxidation activity. Phytochemical analysis of *Mamajjaka* has shown the presence of different flavonoids and alkaloids.^[36, 37]
23. Bhatt NM and others [2009] found the protective effects of *Mamajjaka* for hypoglycemic and antioxidant activity in alloxan induced diabetic neuropathy

in male Charles foster rats. They also found changes in lipid peroxidation (LPO) and anti-oxidant enzymes like SOD, GP_x and CAT levels, decrease in Na-K⁺ ATPase activity were also restored by *Mamajjaka* treatment. This study provides an experimental evidence for the preventive effect of *Mamajjaka* on nerve function and oxidative stress in animal model of diabetic neuropathy. Hence *Mamajjaka* may be clinically tried for treating diabetic neuropathy since it was used as a folklore medicine in diabetic patients.^[38]

AIM:

Understanding the pharmacokinetics of *Mamajjaka* (*Enicostemma littorale* Blume) as a dietary supplement in Diabetes Mellitus.

OBJECTIVES:

Primary objective –

To study *madhumehahar* activity of *Mamajjaka* as a dietary supplement with special reference to antidiabetic mechanism.

Secondary objective –

To study *rasapanchak*, *panchbhoutik* constitution and phytochemical composition of *Mamajjaka*.

OBSERVATIONS:

Mamajjaka widely used in Solapur and Osmanabad districts of Maharashtra, in the form of “leaf pickle” as a dietary supplement in diabetic patient. According to Acharya Priyavat Sharma in Priyavat Nighantu, *Mamajjaka* has predominance of *Tikta rasa*, *Katu vipaka*, *Ushna virya*, *Vayu-Aakash mahabhuta* and *laghu ruksha guna*.^[16] From previous work

done, it is observed that, Mamajjaka contains some anti-diabetic chemical compounds due to which it acts as hypoglycemic agent as well as useful in diabetic complications. These anti-diabetic compounds include, Flavonoids, Saponins, Alkaloids, Steroids, Terpenoids and specially Swertiamarin. It acts in diabetes and related complications by reducing the TBARS (Thiobutyric acid), LPO (Lipid Peroxidase), ROS (Reactive Oxygen Species) damage, LDL (Low Density Lipoprotein) and TG (Triglycerides) levels as well as by increasing CAT (Catalase), GP_x (Glutathione Peroxidase), SOD (Superoxide Dismutase), GSH (Glutathione) anti-oxidant and HDL (High Density Lipoprotein) levels in the serum.

RESULTS:

From previous study, finding is that, *raspanchaka* of *Mamajjaka* helps in *Sampraptibhanga* of *Prameha* especially *Madhumeha*. Also chemical constituents of *Mamajjaka* has significant anti-diabetic potential both in type-1 and type-2 diabetes. As well as it helps to prevent both acute and chronic diabetic complications due to its anti-oxidant, anti-hyperlipidaemic and anti-hyperglycemic property.

DISCUSSION:

According to *Ayurveda*, *rasapanchaka* of *Mamajjaka* helps in *sampraptibhanga* of *Madhumeha*. According to *Acharya Charaka Tikta rasa* reduces the *kledadi dushya* by “moistness (*kleda*), fat with cholesterol (*medo*), adipose tissue (*vasa*), (*majja*), lymph (*lasika*), pus (*puya*), sweat (*sweda*), urine (*mutra*), stool (*purisha*), bile (*pitta*), cough (*shleshma*) absorption (*upshoshanah*)” property^[17], *Katu vipaka* helps to reduce increased *kaphavata dosha*

by “*Shamam ch Kaphavatayoh*” property, *Ushna veerya* reduces the *Kledadi dushya* by *Laghu Ruksha guna* and *Vayvakash mahabhuta* reduces *kledadi dushya* by cleansing (*vishada*), porous (*soushirya*), lightens (*laghavkar*) property.^[18]

From the above study anti-diabetic activity of *Mamajjaka* can be grouped as follows:

1. It reduces Glucose-6-phosphatase activity there by reducing the blood sugar level.
2. It increases the insulin sensitivity by stimulating insulin receptor and increases glucose absorption.
3. It stimulates to pancreatic beta cells for more insulin secretion.
4. It has islet neogenic property of beta cells so increasing insulin secretion.

Its mechanism in preventing diabetic complications also grouped as follows:

1. It acts as anti-oxidant
2. It improves dislipidaemia in blood serum
3. It prevents diabetic nephropathy by reducing renal cholesterol
4. It helps to prevent diabetic neuropathy by reducing nerve damage

CONCLUSION:

From the above study, we can conclude that *Mamajjaka* is in possession of significant anti-diabetic potentials as well as it works as hepato-protective, nephroprotective, cardioprotective and anti-oxidant. Due to the cost-effective, easily available, harmless and palatable properties, we can use *Mamajjaka* as a dietary supplement in the form of “leaves pickle” for diabetic patients in day to day practice. *Mamajjaka* is not only having anti-diabetic potentials, but it also has efficacy against diabetic



complications. These attributes provide the validation for the use of *Mamajjaka* in diabetes by traditional healers in India.

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