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Research Article

THE EFFECTIVENESS OF *KARELA* COMPARED WITH *VIJAYASAR* IN THE MANAGEMENT OF *MADHUMEHA*

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ABSTRACT

Vijayasar (*Pterocarpus marsupium*) has been mentioned in *Charak Samhita*, as a remedy for *Madhumeha* (Diabetes Mellitus). A study conducted by ICMR (Indian Council of Medical Research) revealed that the hypoglycemic effects of *Vijayasar* are comparable to that of tolbutamide. *Karela* (*Mormordica charantia*) is another herb used in *Madhumeha* and it is a routinely used vegetable in Nepal. In this study we measured the effectiveness of *Karela* in patients of *Madhumeha* and compared with that of *Vijayasar*. A total of sixty four patients diagnosed with *Madhumeha* (Fasting Blood Glucose ≥126mg/dl or Post Prandial Blood Glucose≥200mg/dl) were given either *Karela* or *Vijayasar* powder two times a day for one month, along with dietary and lifestyle advices and their blood glucose levels were measured before initiating treatment and after one month of treatment. Changes in the subjective complaints of *Madhumeha* like *Prabhutamutrata, Avilmutrata,* etc. and appearance of adverse events were also evaluated. Randomization of treatment was done and dosage was titrated on the basis of glycemic control and duration of *Madhumeha*. The mean reductions in fasting blood glucose and post prandial blood glucose in *Karela* treated group are 60.83 mg/dl and 79.74 mg/dl respectively and that in *Vijayasar* treated. *Karela* is a safe and effective medicine in the management of *Madhumeha* and it is as effective as *Vijayasar.*

INTRODUCTION

Ayurveda is the science of life which addresses the physical, mental as well as the spiritual aspects of health. *Ayurveda* is the first medical science in which there are vivid descriptions of the diagnosis and management of *Madhumeh*a. *Madhumeha* has been described by *Vagbhatta* as one of the *Maharogas* (difficult to treat diseases.[1] and it is also one of the twenty types of *Prameha* mentioned in *Ayurveda*. *Charak* has mentioned that due to excessive intake of *Nidana* (etiological factors) like *Guru* (heavy), *Snigdha* (oily), *Amla* (sour), *Lavana* (salty) food items; newly harvested food and fresh drinks; excessive sleep, physical inactivity, etc., there is increase in *Kapha, Pitta dosha* and *Meda* (fatty tissue) *Mamsa* (muscle) *Dhatus*. This increased *Kapha, Pitta, Meda* and *Mamsa* obstructs the path of *vata* and causes its abnormality. This disturbed *Vata* carries *Oja* (essence of body) into the *Mutrasaya (Mutravaha-srotas)* and results the disease *Madhumeha*[2]. The clinical features of *Prameha* are *"Prabhutmutrata"* and *"Avilmutrata"* meaning voluminous and frequent excretion of turbid urine. *Madhumeha* is a subtype of *Prameha* so these criteria will also apply to *Madhumeha*. *Charak* has mentioned the specific clinical features of *Madhumeha* as "passage of *Kasaya* (astringent), *Madhura* (sweet*), Pandu* (pale) and *Rukshya* (unoily) urine"[3]. Sushruta has described two types of *Prameha – Sahaj* (genetic) and *Apathyanimittaja* (improper diet/lifestyle induced) and mentioned their clinical features as follows:[4]

1. ***Sahajprameha*:** *Krisha* (thin), *Rukshya* (Dry), *Alpasi* (Eats less), *Pipasubhrisham* (Polydipsia) and *Parisharansheel* (Active habits).
2. ***Apathyanimittaja*:** *Sthula* (Obese), *Bahawasi* (Polyphagia), *Snigdha* (oily skin) and *Saiyaswopna-sheela* (Sits idle, lies down and sleeps).

Vagbhata in *Astanga Hridaya* has described the clinical features of *Madhumeha* as *"madhusamam"* (passage of honey like urine) and "*madhuryachhatano-rata"* (sweetness in the body).[5]

Madhumeha or diabetes mellitus is one of the oldest ailments afflicting human beings. With changing demographics and lifestyle, the prevalence of diabetes is rising exponentially all over the world especially in the developing countries like Nepal. A study conducted in the 7 urban cities of Nepal revealed that the prevalence of diabetes, IGT (impaired glucose tolerance) and IFG (Impaired fasting glucose) was 19.0%, 10.6%, and 9.9 %

respectively in the population aged ≥40 years[6]. The prestigious Journal 'The Lancet' once wrote in its editorial "medicine might be winning the battle of glucose control but it is losing the war against diabetes".[7] This quote largely represents the current scenario, where on one hand there is ever increasing investment in newer interventions for diabetes mellitus and on the other hand its prevalence and subsequent complications are increasing anyway. Diabetes is a metabolic disorder affecting multiple organ systems at the same time. It brings with itself the various metabolic complications of hyperglycemia both acute and chronic affecting almost every organ in our body. It has significant impact on the quality of life of an individual and it adds the burden to the national healthcare as more cases are being added for long term management. As diabetes is often associated with obesity, dyslipidemia, hypertension, insulin resistance, known as metabolic syndrome, an intervention capable of handling all these associated conditions is necessary. Diabetes should never be viewed merely as increased level of blood glucose. Trying to cure lifestyle related chronic diseases (diabetes mellitus) with pharmaceutical medicine is like "trying to dry out a flooded room without turning off the tap". *Ayurveda* promises a perfect solution to this problem as it offers effective modalities of lifestyle management via *Sadvrit*, *Yoga, Dincharya* and *Ritucharya*; and drugs with the potential to act on associated conditions in diabetes like dyslipidemia, hypertension, and obesity besides hyperglycemia.

There are basically two modalities of blood glucose control currently available in the conventional Western Medicine i.e. oral hypoglycemic agents and insulin. Both these agents have numerous side effects which add risks to the health of the patient. The biguanides group of oral hypoglycemic agents (Metformin) commonly causes gastrointestinal disturbances like nausea, diarrhea, abdominal discomfort; and sometimes severe life threatening events like lactic acidosis. The sufonylurea group or the insulin secretagogues cause hypoglycemia as their commonest side effect and other infrequent ones are nausea, skin reactions and abnormal liver function tests. The use of sulfonylurea group of oral hypoglycemic agents has also been associated with adverse coronary artery disease outcome. It has been hypothesized that sulfonylurea prevent vasodilation at the time of myocardial infarction. These insulin secretagogue agents are also supposed to cause beta cell exhaustion and ultimately beta cell failure requiring insulin for blood glucose control. Hypoglycemia is the commonest side effect of insulin therapy besides the hypokalemia which usually occurs in intravenous use. In type two diabetes, there is also possibility of insulin resistance and the dose of insulin keeps on increasing. Being an anabolic hormone, insulin also promotes weight gain and atherosclerosis. *Ayurveda* promises solution to this problem as it offers effective modalities of lifestyle management via *Sadvrit, Yoga, Dincharya* and *Ritucharya;* and drugs with the potential to act on associated conditions in diabetes like dyslipidemia, hypertension, and obesity besides hyperglycemia with fewer side effects if any.The need of a novel drug with equal potency for blood glucose control but without the adverse effects was felt and thus this research was conducted. There are a number of plants described in *Ayurveda* for the management of *Madhumeha* that are both safe and effective. These plants have an advantage of being used in the community for centuries. So, preliminary trials like toxicity studies in animals may not be necessary for them. Clinical trials are necessary to provide evidence base to support or refute their efficacy. Clinical trials to make comparison with conventional medicine as well as to compare two or more *Ayurvedic* medicines need to be carried out. *Karela* and *Vijayasar* have been used for the management of *Madhumeha* for many centuries. Several studies have been conducted around the world on these herbs assessing their effectiveness. Most of these studies showed that these two are effective in controlling blood glucose.[8-12] Large scale randomized controlled trials comparing *Ayurvedic* medicine with conventional medicines can be done to provide evidence of their efficacy. Studies comparing two or more of *Ayurvedic* medicines used for same disease also need to be conducted, so that the choice of drug for a specific condition could be determined.

Vijayasar was not found to have any effect on the lipid profile of the participants[11] while *Karela* showed its effect on lipid profile, serum sialic acid, besides blood sugar[12]. It was found that fruit extract of MC (*Mormordica charantia*), exhibited hypolidemic effect in streptozotocin induced diabetic rats. Though, statistically not significant, there was reduction in body weight and blood pressure in those experimental mice treated with *Karela* [12]. To test the hypothesis that *Karela* induces the same effects on blood glucose of Nepalese population, this study was conducted. The reduction in blood pressure and body weight was also expected in those treated with *Karela*. Some research work has been done regarding the effectiveness of *Vijayasar* in *Madhumeha* in India including some RCTs (Randomized controlled trails)[11], so it has been taken as the reference or standard treatment and *Karela* was taken as experimental treatment.

Objectives

The objectives of this study were to

- To determine the effectiveness of *Karela* (*Mormordica charantia* Linn.) on blood glucose of patients with *Madhumeha* (Diabetes mellitus type II).
- To determine the effectiveness of *Vijayasar* (*Pterocarpus marsupium* Roxb.) on the blood glucose of patients with *Madhumeha* (Diabetes mellitus type II).
- To compare the effectiveness of *Karela* and *Vijayasar* on the blood glucose of patients with *Madhumeha*.

MATERIALS AND METHODS

Study Subjects

Patients diagnosed with *Madhumeha* (type two diabetes mellitus) were taken in and those fulfilling the inclusion criteria were given either *Karela* or *Vijayasar*

for one month. Patients were collected from the OPD (Outpatient Department) and IPD (In Patient Department) of TUATH (Tribhuvan University *Ayurveda* Teaching Hospital), Kirtipur and from various health clinics in Kathmandu at Boudha, Moolpani, Maharajgunj and New road. Ethical approval for this study was obtained from the IRB (Institutional Review Board), IOM, TU. Informed consent was obtained before initiating treatment.

Inclusion Criteria

- Patients with *Madhumeha* (Type II diabetes mellitus) based on ADA Clinical Practice Recommendations 2011 i.e. fasting blood glucose of ≥126mg/dl or post-prandial blood glucose of ≥200mg/dl.
- Patients of age 16-70 years.

Exclusion Criteria

- Fasting blood glucose ≥250.
- BMI≤19 kg/m^2.
- Type 1 diabetes mellitus
- Acute complications of hyperglycaemia like DKA (Diabetic Ketoacidosis), HHS (Hyperglycemic Hyperosmolar State).
- Serum Creatinine ≥2.5 mg/dl.
- Cardiac conditions like Myocardial Infarction, Ischemic Heart Disease.
- Blood Pressure ≥ 180/110mm of Hg.
- Pregnancy or lactation.
- Patients unwilling to give informed consent.

A total sample size of 56 was determined initially for this study but later on considering the randomization sequence to be complete, amendment in the protocol was made 64 subjects were taken.

Interventions

The powder preparation and packaging of *Karela* and *Vijayasar* was done according to the WHO GMP guidelines for herbal medicines at Shivadarshan Herbal Udyog, Dhapasi, Kathmandu Nepal. The dosage of *Karela* powder was 3-6 grams and that of *Vijayasar* was 2-4 grams. Participants were advised to take the medicine half an hour before lunch and dinner with water as *Anupana* (adjunct). Advice regarding *Pathyapathya* (dietary schedule) was also given after inquiring about their dietary habits. Participants were advised to practice *Yoga* i.e. *Pranayama* (breathing exercises) and some *Asana* (postures) like *Mandukasana*, *Paschimottasana, Suryanamaskar.* The baseline data, both subjective and objective was be compared with the end line data after 4 weeks of treatment.

RESULTS AND DISCUSSION

Results

The baseline characteristics of the 64 patients taken in the study are given in table 1. Five patients lost follow up and they could not be contacted for evaluation. Twenty one of the 30 patients receiving *Karela* attained FBG (fasting blood glucose)<130 mg/dl and 12 out of 23 patients whose PPBG (postprandial blood glucose) reports were available, attained a PPBG <180 mg/dl. Two patients in this group lost follow up. Nineteen of the 29 patients receiving attained a FBG of <130 and 14 out of 25 patients whose PPBG reports were available, attained a PPBG value of <180 mg/dl. Three patients in this group lost follow up.

Table 1: Baseline characteristics of patients in *Karela* and *Vijayasar* groups

Characteristics		***Karela* (n=32)**	***Vijayasar* (n=32)**
Age#		52.50±10.48	50.00±9.29
Sex	Male	20	16
	Female	12	16
Duration of diabetes (months)#		12±11.94	24±40.08
Smoking	Current smoker	-	6
	Past smoker	8	8
	Never smoked	24	18
Treatment status	On medications	16	18
	Not on medications	16	14
Activity	Sedentary	21	24
	Moderate	11	8
	Heavy	-	-
Fasting blood glucose*		187.00±41.85	175.16±43.80
Post prandial blood glucose*		258.93±86.01	262.59±70.87
BMI*		26.06±4.89	26.01±30
Systolic blood pressure*		135.50±18.46	136.44±18.38
Diastolic blood pressure*		86.50±11.02	87.19±9.91
***Prabhootmutrata* (Excessive micturition)**		15	13
***Avilmutrata* (Increased turbidity of urine)**		3	3

#median±SD, *mean±SD

There was no significant difference in the BMI of the *Karela* treated (p=0.81) or *Vijayasar* treated (p=0.43) patients. There was statistically significant reduction in Fasting blood glucose and post prandial blood glucose in both *Karela* and *Vijayasar* group. Paired t-test was performed and p value was <0.001.The mean reduction in FBG and PPBG in *Karela* group was 60.83 and 79.74 mg/dl while that in the *Vijayasar* group was 51.34 and 97.72 mg/dl respectively.

There was no statistically significant difference in the blood glucose reductions in both *Karela* and *Vijayasar* group (p=0.273 for FBG and p=0.791 for PPBG).

Paired Samples Test

Drug given		Mean	SD	SEM	CI of the Difference Lower	CI of the Difference Upper	t	df	p
***Karela* powder**	FBG_BT-FBG_AT	60.833	37.322	6.814	46.897	74.769	8.928	29	.000
	PPBG_BT-PPBG_AT	79.739	68.517	14.287	50.110	109.368	5.581	22	.000
***Vijayasar* powder**	FBG_BT-FBG_AT	51.345	36.714	6.818	37.379	65.310	7.531	28	.000
	PPBG_BT-PPBG_AT	97.720	55.951	11.190	74.624	120.816	8.733	24	.000

FBG_AT=Fasting blood glucose before treatment

PPBG_AT=Post-prandial blood glucose after treatment

Pre post MacNemar test was done for analysis of categorical variables like *Prabhootamutrata* and *Avilmutrata* and there statistically significant reduction in both these variables after treatment (p<0.001). A 62 year old female taking *Karela* powder complained of one episode of sweating, shortness of breath, feeling of apprehension at night that was relieved after sweet intake. She was already on sulfonylurea. Another 62 year old female taking *Karela* complained of generalized weakness that disappeared after discontinuing the medicine. A 53 year male taking *Vijayasar* complained of new onset of stiffness of extremities in the morning that was relieved as day progressed. Patient could not be contacted for further evaluation of the complaint, and if it persisted after discontinuation of medicine. There was one case of treatment failure i.e. FBG>250mg/dl despite medication, in *Karela* group.

DISCUSSION

There was statistically and clinically significant reduction in fasting and post-prandial blood glucose in both *Karela* and *Vijayasar* treated group. The reduction in blood glucose was comparable in both groups. *Karela* is supposed to have insulin secreting property so care should be taken while prescribing this drug to a patient with prolonged diabetes, elderly who are at risk of hypoglycemia.

Reduction in BMI was expected in *Karela* treated patients based on previous animal experiment which revealed significant reduction in body weight of *Karela* treated mice. Contradicting this expectation, there was no significant reduction in BMI of those treated with *Karela* or *Vijayasar.* The duration of one month may not be enough to show this effect or the dose of *Karela* may not be enough for weight reduction. Another explanation may be that when blood glucose is brought down by the medication, the catabolic state of hyperglycaemia is corrected and thus regaining the lost body weight of the patient cancelling the weight losing property of *Karela*. *Vijayasar* was reported not to exert any effect on BMI of the patients with diabetes and it was corroborated by this study. The mean reductions in FBG and PPBG after taking *Karela churna* for one month are 60.83 mg/dl and 79.74 mg/dl respectively. There was a reduction of 51.34 mg/dl and 97.72 mg/dl in FBG and PPBG after one month of treatment with *Vijayasar churna.* These reductions in both FBG and PPBG in *Karela* and *Vijayasar* group are not significantly different (p=0.33 and p=0.32 respectively). *Karela* possesses the *Tikta-katu rasa*, *Laghu-rukshya guna* and *Katu vipaka* while *Vijayasar* has *Kasaya-tikta rasa Laghu-rukshya guna* and *Katu vipaka,* which helps to normalize the function of *Jatharagni* and checks the formation of *Bahuabaddha dhatus* by *Soshan* (absorption) of the *Bahudravakaphadosha.*

Diabetes is a chronic ailment and the complications brought about by this disease are the core concern of the treating physician. This study looked into the antidiabetic property of *Karela* and *Vijayasar* for a period of one month only, which is the major limitation besides the small sample size, because diabetes is a chronic disease and needs to be managed with lifelong medications. A bigger study of at least 5-10 years duration could have answered the role of these two drugs in reducing the incidence of the micro vascular and macro vascular complications of diabetes mellitus.

CONCLUSION

This study was the first study of its kind in Nepal which tested the effectiveness of *Karela* and *Vijayasar* in *Madhumeha* and compared the two drugs. The clinical data of this study supports the view that both these drugs are equally potent in controlling blood glucose in patients with *Madhumeha*. There was further evidence that *Karela churna* is as effective as *Vijayasar* in ameliorating the clinical symptoms of *Madhumeha* like *Prabhutamutrata, Avilmutrata,* etc. *Karela churna* reduced FBG and PPBG by a mean of 60.83 mg/dl and 79.74 mg/dl respectively while *Vijayasar churna* reduced FBG and PPBG by a mean of 51.34 mg/dl and 97.72 mg/dl. Although there was a single episode of hypoglycemia like symptoms in this study it is advisable that precaution be taken to avoid the risks of hypoglycemia while prescribing *Karela churna* in elderly, debilitated or patients with long standing diabetes mellitus. Both the *Karela* and *Vijayasar churna* are effective in reducing all symptoms of *Madhumeha* except

Karpadadaha in which there was no significant improvement noted in this clinical trial. Both of the trial drugs showed significant reduction in systolic and diastolic blood pressure and significant proportion of hypertensive patients reverted to normal blood pressure after one month of treatment.

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