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Blood Sugar Lowering Effect of Stem Part of *Berberis aristata* as add on Therapy in Type -2 Diabetes Mellitus Patients

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Original Research Article

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Abstract: Diabetes Mellitus is a metabolic disorders and one of the leading cause of morbidity and mortality. A prospective randomized open parallel group study was conducted in 180 patients of either sex in the age group 40-60 years in medicine department of Muzaffarnagar Medical College. Total 180 patients were divided into 3 groups. Group-1(n=60) was taken as control while group-2(n=60) and group-3(n=60) was taken as test groups and were given *Barberis Arista*. Group 2 patients received 1.5 gm and group 3 patients received 3 gm of *Barberis Arista* respectively as an add on therapy along with the standard oral anti-diabetic treatment. In the study there was improvement and stabilization of glycemic control in test group-2 and 3 when compared with control group ($p < 0.01$). In group-2 and 3 there was reduction in Fasting blood sugar level after 1 month , while post prandial blood sugar[PPBS] level in group 2 was significantly reduced after 2nd month($p<0.01$), but in group -3 there was no significant reduction in PPBS level upto 8th month. Afterwards a significant reduction was seen ($p<0.01$). There was highly significant reduction of HbA1c 3rd month onwards in both test groups ($p<0.001$) So it can be concluded that *Berberis Aristata* as an add on therapy in type 2 DM patients has a beneficial role with regard to the hyperglycemia.
Keywords: Berberis Aristata, PBBS [Post Prandial Blood Sugar].

INTRODUCTION

Diabetes Mellitus [DM] is one of the oldest common metabolic disorders that affect the whole body system. With increasing incidences worldwide, it may be one of the leading causes of morbidity and mortality [1]. Type 2 diabetes is a worldwide health threat and treatment of this disease is limited by availability of effective medications. All of the existing oral hypoglycemic agents have subsequent failure after long term administration. Thus, new oral medications are needed for long-term control of blood glucose in patients with type 2 diabetes. The standard therapy for this epidemic disease includes diet, exercise, use of oral hypoglycemic agents like sulfonylureas, biguanides, phenyl alaninne analogues, thiazolidinediones, α-glucosidase inhibitors etc. and insulin are avaliable for the treatment of diabetes mellitus [2]. Several multicenter trials have demonstrated that different pharmacological agents can successfully lower blood glucose and reduce the risk of developing microvascular and macrovascular diabetic complications. However, the large number of limitations and unwanted side effects that still exist limit their use in clinical practice [3].

From the ancient time, various ethnic and traditional plant medicines have been used to treat diabetes and some of them were clinically proven by various medicinal systems like Ayurveda and Chinese medicines. These herbal drugs were found to be effective in controlling blood glucose levels after thorough investigations and provide active hypoglycemic principles [4]. The world health organization (WHO) has also recommended the evaluation of the effectiveness for various plants treatments of disease conditions where we lack safe modern drugs [5]. Plants have long been a principal source of drugs and now many of the available drugs have been derived directly or indirectly from plants. More than 800 plants may possess anti-diabetic potential according to ethnobotanical information reports [6]. Among the effective herbal derivatives,

Berberis Aristata has aroused great interest for its glucose-lowering activity.

Present study was conducted with aim to evaluate the effect of *Berberis Aristata* on blood sugar level in Type II Diabetes Mellitus in human beings by measuring blood sugar fasting, postprandial and Glycosylated haemoglobin (Hb1AC) in human beings.

MATERIALS AND METHODS

Study desigin

Duration of the study was nine month. It was prospective, randomized, open parallel group study conducted on patient attending the OPD and IPD department of Medicine of MMC Muzaffarnagar. The protocol was approved by Institutional Ethical Committee before starting the study. The informed consent was obtained from each patient and they were fully informed about the aims of the study and about the drug to be given.

Selection of subjects

180 patients with type 2 DM were selected from the department of medicine. The patients were divided into three groups 1,2,3. Group 1[control group] was given standard oral Anti-Diabetic treatment and Test Groups 2 and Group 3 received 1.5gm and 3gm of *B. Aristata* respectively as add on therapy along with oral standard Anti-Diabetic treatment .

Before study the pilot study was done to calculate the testing dose of *B. Aristata*. When the dose above 3gm was given there was unacceptable adverse effect like gastritis, nausea, vomiting and below 1.5 there was no effect on blood sugar.

Inclusion Criteria

Both recently diagnosed male and female patients of the age group between 40-60 years of type 2 DM with moderate physical activity who were on oral anti-diabetic therapy were selected for the study under ideal condition.

Exclusion criteria

Patients having history of coexisting heart disease like hypertension, IHD, liver, kidney, lung or thyroid disorder etc, pregnant women and nursing mothers, female patients taking Oral Contraceptive Pills, patients on steroids, Patients with other types of Diabetes mellitus e.g. Gestational diabetes , drug induced diabetes, smoker, athelets, complicated cases.

MATERIAL

Berberis aristata

Dried stem powder of *Berberis Aristata* was obtained from Bhartiya ayurvedic pharmacy, Delhi. This dried powder form of *Berberis Aristata* were given to the patients in a dose of 1.5gm and 3gm in two divided doses daily, to be given empty stomach at least 30 minutes before breakfast and dinner. This dried powder form of *Berberis Aristata* was stored in room temperature in an air tight container. The hypoglycemic symptoms were explained to the patients and the emergency precautionary measures were also explained to overcome it.

STUDY PROTOCOL AND TREATMENTS

All participants were instructed to follow their usual hypo-caloric, low-glycemic index diet throughout the study. The controlled-energy diet (a daily caloric deficit of about 600 kcal) was based on the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III recommendations 26 and contained 50% of calories from carbohydrates, 30% from fat (7% saturated fat, up to 10% polyunsaturated fat, and up to 20% monounsaturated fat), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fiber. Standard diet advice was provided by a dietician and/or specialist physician. The participants were also encouraged to maintain their usual standard physical activity (riding a stationary bike for 20 to 30 minutes, three to four times a week or brisk walking for 30-minute sessions, three to four times a week). All the enrolled patients were divided to either of three groups, Group-1 received standard oral antidiabetic while Group-2 and Group-3 received 1.5gm and 3gm of stem powder of Berberis aristata in two divided doses (before breakfast and dinner) with oral antidiabetic drugs as add on therapy respected for the whole length of the study (9 months)[9]. Patients were asked to maintain the treatment diary and was strictly advised how to take medication.

CONCOMITANT ANTIDIABETIC THERAPIES

The glycemic control of the participants of all groups was suboptimal despite a prescribed diet, physical exercise and hypoglycemic drugs. In group-1 (control), 16were on metformin mono therapy, 6 were on sulfonylureas and 34 were on oral combination therapy (24 with metformin and sulfonylureas and 10 with metformin plus dipeptidyl peptidase-4[DPP-4] inhibitors) and 4 with metformin plus sulfonylurea and pioglitazone.

In group-2, 6 were on metformin mono therapy, 4 were on sulfonylureas and 44 were on oral combination therapy (40 withmetformin and sulfonylureas and 4 with metformin plus sulfonylureas and dipeptidyl peptidase-4[DPP-4] inhibitors) and 6 with metformin plus sulfonylurea and pioglitazone.

In group-3, 7 were on metformin mono therapy, 3 were on sulfonylureas and 26 were on oral combination therapy (19 with metformin and sulfonylureas and 4 with metformin plus sulfonylureas and dipeptidyl peptidase-4[DPP-4] inhibitor, 3 with metformin plus α Glucosidase inhibitors and 24with

metformin plus sulfonylurea and pioglitazone.

Collection of sample

All plasmatic variables were determined after a 12 hour overnight fast. Venous blood samples were drawn from all patients between 8:00 and 9:00 am for FBS, HbA1c, and for PPBS after 2 hour again blood sample were drawn for investigation.

Investigations

All estimations were done in the Biochemistry department of MMC Muzaffarnagar. Estimation of Fasting and post prandial (p.p) blood sugar levels was done initially on alternate days and then weekly by Glucose Oxidase method/ Peroxidase method [10]. Estimation of Glycosylated Hemoglobin (HbA1C) was done initially and then every three months using Ion Exchange Resin method [11].

Treatment tolerability was assessed in the patients and the comparison of clinical and laboratory values with baseline levels. Safety monitoring included physical examination, vital sign assessment, weight, electrocardiogram, and adverse event recording.

STATISTICAL ANALYSIS

The data obtained were statistically analyzed by using unpaired t-test as the comparison of two sets of observation of same characteristic are obtained.

RESULTS AND OBSERVATIONS

A prospective, stratified randomization done on the basis of age and gender, open parallel group study was conducted in total 180 patients of either sex in the age group of 40-60 years attending the outpatient/ indoor department of Medicine of MMC&H, Muzaffarnagar Medical College, Muzaffarnaga. A total of 180 patients were randomized into three groups of 60 each, group-1(n=60) was taken as control while group-2(n=60) and group-3(n=60) was taken as study group who had received 1.5gm and 3gm of *Berberis Aristata* respectively as add on therapy along with their conventional anti-Diabetic treatment. In table 1 FBS, Table2 PPBS, Table 3 HbA1C results are shown.

Table-1: Unpaired t-test b/w group-1, group-2 and group 3 of FBS Parameter

Days/ Months	Group1 Mean±2SD	Group2 Mean±2SD	P value 1&2 group	Group 3 Mean±2SD	P value 1&3 group
On 1 st day	164.97±17.14	164.40±13.78	>0.05	160.97±14.90	>0.05
After 1 month	146.00±14.88	139.23±17.30	<0.001	133.83±15.34	<0.001
After 2 month	136.97±10.58	119.37±13.62	<0.001	109.20±11.86	<0.001
After 3 month	134.73±10.12	108.83±18.30	<0.001	95.73±15.06	<0.001
After 4 month	134.63±9.74	104.63±18.00	<0.001	89.67±16.24	<0.001
After 5 month	135.20±9.02	100.73±12.86	<0.001	86.97±11.22	<0.001
After 6 month	133.67±9.88	99.53±18.32	<0.001	85.77±13.52	<0.001
After 7 month	134.70±9.82	97.27±15.42	<0.001	86.30±13.80	<0.001
After 8 month	132.77±7.74	97.10±11.14	<0.001	86.80±12.46	<0.001
After 9 month	131.70±9.64	92.50±13.14	<0.001	81.30±8.48	<0.001

Table-2: Unpaired t-test b/w group1-, group-2 and group 3 of PPBS Parameter

Days/ Months	Group1 Mean±2SD	Group2 Mean±2SD	P value 1&2 group	Group 3 Mean±2SD	P value 1&3 group
On 1 st day	249.17±20.30	255.00±23.08	>0.05	253.27±21.34	>0.05
After 1 month	210.83±20.06	186.30±32.46	<0.001	186.40±27.96	<0.001
After 2 month	186.03±17.70	144.60±21.28	<0.001	141.90±23.44	<0.001
After 3 month	173.63±21.72	130.93±7.62	<0.001	127.83±9.78	<0.001
After 4 month	172.30±15.52	136.00±9.86	<0.001	129.50±11.84	<0.001
After 5 month	169.03±14.82	136.87±17.66	<0.001	126.33±8.66	<0.001
After 6 month	166.07±12.38	135.30±12.92	<0.001	124.93±9.20	<0.001
After 7 month	163.23±9.88	136.83±10.36	<0.001	125.53±10.28	<0.001
After 8 month	161.70±5.58	133.37±9.04	<0.001	126.60±9.28	<0.001
After 9 month	161.57±6.58	127.37±4.44	<0.001	124.63±6.48	<0.001

Table-3: Unpaired t-test b/w group-1, group-2 and group 3 of HbA1C Parameter

Days/ Months	Group1 Mean±2SD	Group2 Mean±2SD	P value 1&2 group	Group 3 Mean±2SD	P value 1&3 group
On 1 st day	7.98±0.50	7.82±0.54	<0.01	7.84±0.66	>0.05
After 3 month	7.31.00±0.58	6.89±0.82	<0.001	6.57±0.62	<0.001
After 6 month	6.67±0.38	6.35±0.36	<0.001	6.08±0.32	<0.001
After 9 month	6.40±0.32	6.03±0.32	<0.001	5.84±0.30	<0.001

DISCUSSION & CONCLUSION

Berberis Aristata belongs to family Berberidaceae and widely distributed in evergreen regions of temperate and sub- tropical. *Berberis* has about 650 species worldwide, of which 54 have been reported from Indian Himalaya, especially in state of Uttarakhand. Berberis Aristata is used in Ayurveda medicines from very longtime [12, 13].

It was *report the anti hyperglycaemic activity of stem bark of B. Aristata, the methanolic extract of stem bark of B. Aristata to exhibit significant anti-diabetic activity* in a dose dependent manner with substantial reducing power which affords protection in alloxan induced diabetic rats [15]. It showed acute toxicity tests that shows the drug is free of toxic effects at 500mg/kg body weight and given intra peritoneally[16].

Several studies, mostly performed in the Chinese population, have reported the effects of berberine on the lipidic and glycemic profile [17, 18], but very few have reported the effect of berberine in Caucasians [19-21]. In another study with conventional hypoglycemic drugs produced only suboptimal control in blood sugar and lipid levels or unacceptable adverse effect. In order to establish scientific basis for the utility and safety of this plant in the treatment of diabetes, it was decided to evaluate the hypoglycemic and hypolipidimic activity of *Berberis Aristata* DC on type 2 DM patients as add on therapy.

The administration of powder of *Berberis Aristata* at 1.5g and 3g daily dose as add on therapy in patients of group-2 and group-3 produced a highly significant reduction and stabilization of glycemic control ($p<0.001$) when compared with their respective control from 1 month onwards till the end of the study both in the Fasting Blood Sugar as well as in the Post Prandial Blood Sugar (table-1, 2). The similar change was found in the HbA1c levels also starting from 3rd month of the administration. ($p<0.001$). (Table-3)

This anti-diabetic effect of *B. Aristata* may be attributed to the constituients berberine, berbamine and palmitine, among them most probably with berberine alkaloid, as in the previous study itwas reported Berberine regulates glucose metabolism through multiple mechanisms of action: 1) stimulation of glucose uptake by glucose transporter type 4 (GLUT-4) upregulation; 2) activation of 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK), as a consequence of theinhibition of mitochondrial function; 3) suppression of adipogenesis, by inhibiting peroxisome proliferator-activated receptor gamma (PPARγ) and C-enhancer-binding protein alpha (C/EBPα) function; 4) stimulation of glucagon-like peptide-1 (GLP-1) release from ileal cells; 5) suppression of human protein tyrosine phosphatase 1B (h-PTP 1B); 6) stimulation of the pancreatic G protein-coupled receptor 40 (GPR40); and 7) reduction of intestinal glucose absorption, by inhibiting α-glucosidase activity[22].

It also has shown the sugar lowering effect of *Berberis Aristata* by inhibiting DPP-IV enzyme. Apart from the DPP-IV inhibition, it also shows other antidiabetic properties like insulin mimetic, reduction of insulin resistance, glycolysis promotion and enhancing the GLP-I release. Berberine significantly reduced the fasting blood glucose (FBG), HbA1c, and triglycerides in type 2 diabetic patients. It lowered blood glucose level through increasing insulin receptor expression. Berberine is preferred over metformin for hypoglycemic patients with liver diseases. Ethanol extract of the roots of *Berberis Aristata* had shown effective reduction in serum glucose along with increase in HDL cholesterol level in alloxan induced diabetic rats [23].

Free radicals of different forms are constantly generated for specific metabolic requirement and quenched by an efficient antioxidant network in body. When the generation of these species exceeds the levels of antioxidant mechanism, it leads to oxidative damage of tissues and biomolecules, eventually leading to disease conditions like Diabetes Mellitus. *Berberis Aristata* has antioxidant property; this appears to be a reflection of reduced oxidative stress. In diabetes mellitus as it promotes the destruction of β-cells of pancreas thereby affecting the production of insulin and also attenuating the peripheral action of insulin on glucose transport and metabolism in skeletal muscle [24]. Another study also revealed that 50% ethanolic extracts of the root showed significant blood glucose lowering effect combined with increased catalase, super oxide dismutase, glutathione peroxidase, glutathione reductase activity[16].

It is significant to note that the *Berberis Aristata* as add on therapy exhibited no major or life threatening adverse effect in our study. Minor side effects like -nausea, 1.11% flatulence, 3.33% diarrhoea, 1.11% constipation, 2.22% rashes, 4.44% headache, 4.44% abdominal pain, 3.33% metallic taste, 1.11% anorexia and 1.11% weight gain were reported. These minor side effects do not demand the withdrawl of *Berberis Aristata* add on therapy and could be safely ignored.

CONCLUSION

Berberis Aristata as an add on therapy in type 2 DM patients has a beneficial role with regard to the hyperglycemia and very safe as no major side effects was observed affecting morbidity and mortality. So *Berberis Aristata* as an add on therapy could represent a good treatment option before increasing oral antidiabetic dose or initiating insulin therapy in diabetic patients with suboptimal glycemic control. Limitation of the study is that lipid profile was not

considered in the study because of limitation of the funds for the study. Further lipid lowering and molecular study may be done.

REFERENCES

1. Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. Harrison's Principles of Internal Medicine, 15th ed. McGraw Hill Medical: New York, 2001.
2. Hoffmann IS, Roa M, Torrico F, Cubeddu LX. Ondansetron and metformin-induced gastrointestinal side effects. *Am J Ther*. 2003;10(6):447–451.
3. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457–2471.
4. Li WL, Zheng HC, Bukuru J, De Kimpe N. Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. Journal of ethnopharmacology. 2004 May 1;92(1):1-21.
5. Rang HP, Dale MM, Ritter JM, and Flower RJ. *Rang and Dale's Pharmacology*, 6th ed. Churchill Livingstone: London, 2007.
6. Ismail MY. Clinical evaluation of antidiabetic activity of Trigonella seeds and Aegle marmelos leaves. World Applied Sciences Journal. 2009;7(10):1231-4.
7. Dong H, Zhao Y, Zhao L, Lu F. The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials. *Planta Med*. 2013;79(6):437–446.
8. Dong H, Wang N, Zhao L, Lu F. Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. *Evid Based Complement Alternat Med*. 2012;2012:591–654.
9. National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25).
10. Tescher A and Richtench P. schweiz Med. wschr. 1971: 101: 345 and 390
11. Trivelli LA, ranney LA, Ranney HM and Lai HT. New Eng.J.Med.284,353;1971.
12. Ali M, Malik AR, Sharma KR. Vegetative propagation of Berberis aristata DC. An endangered Himalayan shrub. Journal of Medicinal Plants Research. 2008 Dec 31;2(12):374-7.
13. Komal S, Ranjan B, Neelam C, Birendra S, Kumar SN. Berberis aristata: A review. Int J Res Ayurveda Pharm. 2011;2(2):383-8.
14. The Ayurvedic pharmacopoeia of India, Government of India, Ministry of health and family Welfare department of AYUSH, New Delhi, 2007; 2(I): 34-6.
15. Gupta JK, Mishra P, Rani A, Mazumder PM. Blood glucose lowering potential of stem bark of Berberis aristata Dc in alloxan-induced diabetic rats. Iranian Journal of Pharmacology and therapeutics 2010; 9: 21-24
16. Singh J, Kakkar P. Antihyperglycaemic and antioxidant effect of Berberis aristata root extracts and its role in regulating carbohydrate metabolism in diabetic rats. Journal of Ethnopharmacology 2009; 123:22-26
17. Dong H, Wang N, Zhao L, Lu F. Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. Evid Based Complement Alternat Med. 2012;2012:591–654.
18. Derosa G, Maffioli P, Cicero AF. Berberine on metabolic and cardiovascular risk factors: an analysis from preclinical evidences to clinical trials. Expert Opin Biol Ther. 2012;12(8):1113–1124
19. Di Pierro F, Villanova N, Agostini F, Marzocchi R, Soverini V, Marchesini G. Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control. Diabetes Metab Syndr Obes. 2012;5:213–217.
20. Orio F, Muscogiuri G, Palomba S, Savastano S, Volpe A, Orio M, Colarieti G, La Sala GB, Colao A, Marciano F, Ascione A. Berberine improves reproductive features in obese Caucasian women with polycystic ovary syndrome independently of changes of insulin sensitivity. e-SPEN Journal. 2013 Oct 1;8(5):e200-4.
21. Hu Y, Ehli EA, Kittelsrud J, Ronan PJ, Munger K, Downey T, Bohlen K, Callahan L, Munson V, Jahnke M, Marshall LL. Lipid-lowering effect of berberine in human subjects and rats. Phytomedicine. 2012 Jul 15;19(10):861-7.
22. Yin J, Zhang H, Ye J. Traditional Chinese medicine in treatment of metabolic syndrome. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 2008 Jun 1;8(2):99-111.
23. Chakrabarti R, Bhavtaran S, Narendra P, Varghese N, Vanchhawng L, Mohamed Sham Shihabudeen H, Thirumurgan IV K. Dipeptidyl peptidase-IV inhibitory activity of Berberis aristata. J Nat Prod. 2011;4:158-63.
24. Paolisso G, Gambardella AN, Tagliamonte MR, Saccomanno F, Salvatore TE, Gualdiero P, D'Onofrio MV, Howard BV. Does free fatty acid infusion impair insulin action also through an increase in oxidative stress?. The Journal of Clinical Endocrinology & Metabolism. 1996 Dec 1;81(12):4244-8.