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RESEARCH ARTICLE

Evaluation of hypolipidemic effect of stem part of *Berberis aristata* in Type 2 diabetes mellitus patients as add on therapy

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ABSTRACT

Background: Diabetes mellitus (DM) is one of the oldest common metabolic disorders characterized by hyperglycemia, hyperlipidemia, negative nitrogen balance, and ketonemia. It is a one of the most important pathological conditions associated with dyslipidemia that affects the whole body system. Several types of DM exist and result by a complex interaction of genes and drugs, gestational diabetes, environmental factors such as stress and sedentary lifestyle choices. DM is the leading cause of end-stage renal disease, coronary artery disease, cerebrovascular disease, nontraumatic lower extremity amputations, and adult blindness. **Aims and Objectives:** This study was conducted to evaluate the hypolipidemic effect of stem part of *Berberis aristata* in patients of Type 2 DM with dyslipidemia as add on therapy. **Materials and Methods:** A prospective randomized open parallel group study was conducted in total 90 patients having high fasting blood sugar (FBS) and dyslipidemia of either sex in the age group of 30-60 years attending of outpatient/indoor Department of Medicine of Muzaffarnagar Medical College and Hospital, Muzaffarnagar, Uttar Pradesh, India. A total of 103 each Group 1 ($N = 30$) was taken as control while Group 2 ($N = 30$) and Group 3 ($N = 30$) was taken as study group who had received 1.5 and 3 g of *B. aristata,* respectively, as add on therapy along with their conventional antidiabetic and antihyperlipidemic (in certain number of patients) treatment. During the study, 13 patients (8 male and 5 female) did not complete the study and reason of premature withdrawal included protocol violation. **Results:** In our study, there were a statistically a highly significant improvement and stabilization of glycemic control in test Groups 2 and 3 when compared with control group ($P < 0.01$). In Groups 2 and 3, reduction of FBS level from 1 month onward. The mean high density lipoprotein level improved significantly in the Group 2 ($P < 0.01$) and highly significantly in Group 3 ($P < 0.001$) as compared to control. The mean total cholesterol level decreased no significantly in the Group 2 ($P > 0.05$) and highly significant in Group 3 ($P < 0.001$) as compared to control. The mean triglyceride level decreased highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control. The mean low density lipoprotein level decreased highly significant in the Group 2 and Group 3 ($P < 0.001$) as compared to control. **Conclusion:** It can be concluded that *B. aristata* as an add on therapy in Type 2 DM patients has a beneficial role with regard to the hyperglycemia and dyslipidemia very safe as no major side effects were observed affecting morbidity and mortality. Hence, *B. aristata* as an add on therapy could represent a good treatment option before initiating insulin and hypolipidemic therapy in diabetic patient with suboptional glycemic and lipideimic control to avoid unwanted adverse effects and can cut down cost of treatment.

KEY WORDS: Type 2 Diabetes Mellitus; Dyslipidemia *Berberis aristata*; Add on Therapy

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INTRODUCTION

In both developed and underdeveloped countries, the prevalence of noncommunicable diseases is gaining more significance among the adult population. Globally, deaths of many people yearly are caused by cardiovascular diseases (CVDs) than any other causes.[1] Dyslipidemia is elevation

of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein (HDL) level that contributes to the development of atherosclerotic CVD, including acute coronary syndrome, stroke, transient ischemic attack or peripheral arterial disease presume caused by atherosclerosis. The primary (genetic) causes and secondary (lifestyle and other) causes contribute dyslipidemia in very degrees. The primary causes are single or multiple gene mutation that results in either or production or defective clearance of TG and low density lipoprotein (LDL) cholesterol, or in under production or excessive clearance of HDL while secondary causes contribute to many cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats. Other common secondary causes include diabetes mellitus (DM), alcohol overuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis, and other cholestasis liver diseases, drugs such as thiazides, β-blockers, retinoids, and highly active antiretroviral.

Secondary causes of low levels of HDL cholesterol include cigarette smoking, anabolic steroids, HIV infection, and nephrotic syndrome.[2]

The effects of unhealthy diet and physical inactivity may show up in individuals such as elevated blood pressure, increased blood glucose, raised blood lipids, and overweight and obesity.[1] Advancing technology and drastic lifestyle changes have been associated with rise in various noncommunicable disorders, including DM.[3] It is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance, and sometimes ketonaemia. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.[4] Diabetes is an especially significant secondary cause because patients tend to have an atherogenic combination of high TGs; high small, dense LDL fractions; and low HDL (diabetic dyslipidemia, hypertriglyceridemic hyperapo B). Patients with Type 2 diabetes are especially at risk. The combination may be a consequence of obesity, poor control of diabetes, or both, which may increase circulating free fatty acids, leading to increased hepatic very LDL (VLDL) production. TG-rich VLDL then transfers TG and cholesterol to LDL and HDL, promoting formation of TG-rich, small, dense LDL, and clearance of TG-rich HDL. Diabetic dyslipidemia is often exacerbated by the increased caloric intake and physical inactivity that characterize the lifestyles of some patients with Type 2 diabetes. Women with diabetes may be at special risk of cardiac disease from this form.[5]

DM is one of the oldest common metabolic disorders that affect the whole body system. Several types of DM exist and result by a complex interaction of genes and drugs, gestational diabetes, environmental factors such as stress and sedentary lifestyle choices. DM is the leading cause of end-stage renal disease, nontraumatic lower extremity amputations, and adult blindness. With increasing incidences worldwide, DM will likely continue to be a leading cause of morbidity and mortality for the foreseeable future.[4]

According to the World Health Organization (WHO), Type 2 diabetes is the World's fifth leading cause of death and it is estimated that it will be surpass 366 million by the year 2030.[6]

The standard therapy for this epidemic disease includes diet, exercise, use of oral hypoglycemic agents such as sulfonylureas, biguanides, phenyl alaninne analogs, thiazolidinediones, and α-glucosidase inhibitors are available along with insulin and lipid lowering drugs for the treatment of DM.[7] Several multicenter trials have demonstrated that different pharmacological agents can successfully lower blood glucose, lipids and lipoproteins 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.[8]

From the ancient time, various ethnic and traditional plant medicines have been used to treat this metabolic disorder, and some of them were clinically proven by various medicinal systems such as 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.[9] The WHO has also recommended the evaluation of the effectiveness for various plants' treatments of disease conditions where we lack safe modern drugs.[10] 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 antidiabetic potential according to ethnobotanical information reports.[11] Consequently, a small, albeit significant, and proportion of diabetic patients are also advised to resort to complementary and alternative medical therapies. Among the effective herbal derivatives, *Berberis aristata* has aroused great interest for its glucose-lowering and lipid-lowering activity.

This study was conducted with the aim to evaluate the effect of *B. aristata* on lipid profile including fasting sugar level in Type 2 DM in human beings.

MATERIALS AND METHODS

Study Design

This 9 months study was prospective, randomized, open parallel group study conducted on patient having high fasting

blood sugar (FBS) and dylipidemia attending the outpatient/ indoor Department of Medicine of Muzaffarnagar Medical College and Hospital, Muzaffarnagar to evaluate therapeutic efficacy of *B. aristata* in Type 2 DM. The protocol was approved by the Institutional Ethical Committee before starting the study. It was carried out between April 2013 and October 2014 (April 29, 2013 - October 01, 21014). 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

Suitable patients were contacted in the Department of Medicine. 103 patients diagnosed with Type 2 DM were enrolled. All patients provided their written informed consent to participate in this study after full explanation of the study had been given. 90 patients completed the study. The patients were divided into three groups. One group was given only antidiabetic treatment (control group) and other Groups 2 and 3 had received 1.5 and 3 g of *B. aristata,* respectively, as add on therapy along with their conventional antidiabetic treatment.

Inclusion Criteria

Both male and female patients of the age group between 30 and 60 years of Type 2 DM who were on oral antidiabetic therapy only were selected randomly for the study.

Exclusion Criteria

The patients having a history of coexisting heart, 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 DM, e.g., gestational diabetes, drug-induced diabetes.

Materials

B. aristata

Dried stem powder of *B. aristata* was obtained from Bhartiya Ayurvedic Pharmacy, Delhi. This dried power form of *B. aristata* was given to the patients in a dose of 1.5 and 3 g in two divided doses daily, to be given empty stomach at least 30 min before breakfast and dinner. This dried powder form of *B. aristata* was stored in room temperature in an airtight 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 hypocaloric, low-glycemic, and low-lipidemic 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 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 20-30 min, 3-4 times a week or brisk walking for 30 min sessions, 3-4 times a week). All the enrolled patients were randomized to either of three groups, Group 1 received conventional oral antidiabetic while Groups 2 and 3 received 1.5 and 3 g of stem powder of *B. 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).[12]

Concomitant Antidiabetic and Hypolipidemic 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), 8 were on metformin mono therapy, three were on sulfonylureas, and 22 were on oral combination therapy (17 with metformin and sulfonylureas and three with metformin plus dipeptidyl peptidase-4 (DPP-4) inhibitors and two with metformin plus sulfonylurea and pioglitazone). 19 patients in the Group 1 were on statin monotherapy. 14 participants were not taking any hypolipidemic treatment.

In Group 2, six were on metformin mono therapy, two were on sulfonylureas, and 28 were on oral combination therapy (23 with metformin and sulfonylureas and two with metformin plus sulfonylureas and DPP-4 inhibitors and three with metformin plus sulfonylurea and pioglitazone). 21 patients in the Group 2 were on statin mono therapy. 15 participants were not taking any hypolipidemic treatment.

In Group 3, seven were on metformin mono therapy, one were on sulfonylureas, and 26 were on oral combination therapy (19 with metformin and sulfonylureas and two with metformin plus sulfonylureas and DPP-4 inhibitor, two with metformin plus α-glucosidase inhibitors and 11 with metformin plus sulfonylurea and pioglitazone. 16 patients in the Group 3 were on statin mono therapy. 18 participants were not taking any hypolipidemic treatment.

Collection of Sample

All plasmatic variables were determined after a 12 h overnight fast. Venous blood samples were drawn from all patients between 8:00 and 9:00 am for FBS, HDL, LDL, TG were drawn for investigation.

Investigations

All estimations were done in the Biochemistry Department of Muzaffarnagar Medical College and Hospital, Muzaffarnagar. Estimation of FBS Levels was done initially on alternate days and then weekly by glucose oxidase method/peroxidase method.[13] Estimation of lipid profile was done initially and then every 3 months as follows:

- HDL by phosphotungstate method,[14]
- Total cholesterol (TC) by enzymatic method,[15]
- TG by enzymatic method,[16]
- LDL by Friedewald method.[17]

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.

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 using unpaired *t*-test.

RESULT

A prospective, randomized, open parallel group study was conducted in total 90 patients of either sex in the age group of 30-60 years attending the outpatient/indoor Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar. A total of 103 patients were enrolled in the trial. Of these 90 patients completed the study. A total of 90 patients were randomized into three groups of 30 each, Group 1 ($N = 30$) was taken as control while Group 2 ($N = 30$) and Group 3 ($N = 30$) was taken as study group who had received 1.5 and 3 g of *B. aristata*, respectively, as add on therapy along with their conventional antidiabetic and hypolipidemic (in number of patients) treatment. During the study 13 patients (8 males and 5 females) did not completed the study and the reason for premature withdrawal included protocol violation, failure to follow-up or noncompliance.

Effect on Blood Glucose Level

In our study, baseline mean FBS at day 1 in Group 1 (control), Group 2, and Group 3 was 164.97 ± 17.14, 164.40 ± 13.78, and 160.97 ± 14.90. There was no significant difference between the FBS level of the three groups. After 1 month, the mean FBS of patients in Group 1, Group 2, and Group 3 was 146.0 ± 14.88, 139.23 ± 17.30, and 133.83 ± 15.34, respectively. There was a highly significant reduction in the FBS levels in Group 2 and Group 3 ($P < 0.001$) as compared to their initial value before starting the *B. aristata* administration. After 2 months, the mean FBS of patients in Group 1, Group 2, and Group 3 was 136.97 ± 10.58, 119.37 ± 13.62, and 109.20 ± 11.86, respectively. The FBS reduced highly significantly in the Group 2 and Group 3 ($P <0.001$) as compared to control. After 3 months, the mean FBS of patients in Group 1, Group 2, and Group 3 was 134.73 ± 10.12, 108.83 ± 18.30, and 95.73 ± 15.06, respectively. The FBS levels reduced highly significantly in the Group 2 and Group 3($P < 0.001$) as compared to control. After 4 months, the mean FBS level of patients in Group 1, Group 2, and Group 3 was 134.63 ± 9.74, 104.63 ± 18.00, and 89.67 ± 16.24, respectively. The FBS levels reduced highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control. After 5 months, the mean FBS of patients in Group 1, Group 2, and Group 3 was 135.20 ± 9.02, 100.73 ± 12.86, and 86.97 ± 11.22, respectively. The FBS reduced highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control.

After 6 months, the mean FBS of patients in Group 1, Group 2, and Group 3 was 133.67 ± 9.88, 99.53 ± 18.32, and 85.77 ± 13.52, respectively. The FBS levels reduced highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control. After 7 months, the mean FBS of patients in Group 1, Group 2, and Group 3 was 134.70 ± 9.82, 97.27 ± 15.42, and 86.30 ± 13.80, respectively. The FBS levels reduced highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control. After 8 months, the mean FBS of patients in Group 1, Group 2, and Group 3 was 132.77 ± 7.74, 97.10 ± 11.14, and 86.80 ± 12.46, respectively. The FBS levels reduced highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control. After 9 months, the mean FBS of patients in Group 1, Group 2, and Group 3 was 131.70 ± 9.64, 92.50 ± 13.14, and 81.30 ± 8.48, respectively. The FBS levels decreased highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control (Tables 1 and 2).

Effect on Lipid Profile

The lipid profile was measured at every 3 months interval up to 9 months. Initially, baseline mean HDL levels at day 1 in Group 1 (control), Group 2, and Group 3 were 39.43 ± 4.58, 39.57 ± 4.28, and 39.70 ± 3.90, respectively. After 3 months, the mean HDL levels of patients in Group 1 and Group 2, Group 3 were 41.93 ± 3.92 and 42.40 ± 4.08, 42.67 ± 3.90, respectively. The mean HDL level improved no significantly in the Group 2 and Group 3 ($P > 0.05$) as compared to control. After 6 months, the mean HDL levels of patients in Group 1 (control) and Group 2, Group 3 were 43.47 ± 3.70 and 44.17 ± 3.94, 45.37 ± 4.42, respectively. The mean HDL level improved no significantly in the Group 2 ($P > 0.05$) and

highly significantly in Group 3 ($P < 0.001$) as compared to control. After 9 months, the mean HDL levels of patients in Group 1 and Group 2, Group 3 were 43.73 ± 4.06 and 44.90 ± 3.76, 46.43 ± 4.36, respectively. The mean HDL level improved significantly in the Group 2 ($P < 0.01$) and highly significantly in Group 3 ($P < 0.001$) as compared to control (Tables 3 and 6).

The TC level initially in Group 1, Group 2, and in Group 3 was 204.90 ± 44.88, 217.87 ± 37.34, and 219.90 ± 13.52, respectively. While at 3 months, the mean TC levels of patients in Group 1, Group 2, and Group 3 were 198.63 ± 19.56, 201.77 ± 20.12, and 201.90 ± 13.66, respectively. The mean TC level decreased no significantly in the Group 2 and Group 3 ($P > 0.05$) as compared to control. After 6 months, the mean TC levels of patients in Group 1 (control), Group 2, and Group 3 were 189.13 ± 19.06, 189.80 ± 19.24, and 184.43 ± 14.30, respectively. The mean TC level decreased no significantly in the Group 2 ($P > 0.05$) and significantly in Group 3 ($P < 0.01$) as compared to control. After 9 months, the mean TC levels of patients in Group 1, Group 2, and Group 3 were 185.87 ± 18.74, 184.37 ± 17.40, and 176.37 ± 15.92, respectively. The mean TC level decreased no significantly in the Group 2 ($P > 0.05$) and highly significantly in Group 3 ($P < 0.001$) as compared to control (Tables 8 and 10).

The mean TGs levels at day 1 in Group 1, Group 2 and in Group 3 was 179.70 ± 16.84, 184.47 ± 15.66, and 192.13 ± 11.64 but at 3 months the mean TG levels of patients in Group 1, Group 2, and Group 3 was 170.43 ± 14.50, 169.73 ± 15.58, and 168.87 ± 11.76, respectively. The mean TG level decreased no significantly in the Group 2 and Group 3 ($P > 0.05$) as compared to control. After 6 months, the mean TG levels of patients in Group 1, Group 2, and Group 3 was 161.87 ± 14.70, 157.70 ± 16.86, and 146.27 ± 13.66, respectively. The mean TG level decreased significantly in the Group 2 ($P < 0.01$) and highly significantly in Group 3 ($P < 0.001$) as compared to control. After 9 months, the mean TG levels of patients in Group 1, Group 2, and

Table 1: Unpaired *t*-test between Group 1 (control) and Group 2 of FBS parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 2 (*N*=30)				
On 1st day	164.97±17.14	164.40±13.78	95	58	0.284	*P*>0.05 (N/S)
After 1st month	146.00±14.88	139.23±17.30	95	58	3.251	*P*<0.001 (H/S)
After 2nd month	136.97±10.58	119.37±13.62	95	58	11.184	*P*<0.001 (H/S)
After 3rd month	134.73±10.12	108.83±18.30	95	58	13.574	*P*<0.001 (H/S)
After 4th month	134.63±9.74	104.63±18.00	95	58	16.048	*P*<0.001 (H/S)
After 5th month	135.20±9.02	100.73±12.86	95	58	24.046	*P*<0.001 (H/S)
After 6th month	133.67±9.88	99.53±18.32	95	58	17.958	*P*<0.001 (H/S)
After 7th month	134.70±9.82	97.27±15.42	95	58	22.428	*P*<0.001 (H/S)
After 8th month	132.77±7.74	97.10±11.14	95	58	28.831	*P*<0.001 (H/S)
After 9th month	131.70±9.64	92.50±13.14	95	58	26.343	*P*<0.001 (H/S)

HS: Highly significant, S: Significant, NS: Not Significant, C.I.: Confidence interval, d.f.: Degree of freedom, SD: Standard deviaion

Table 2: Unpaired *t*-test between Group 1 (control) and Group 3 of FBS parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (Control) (*N*=30)	Group 3 (*N*=30)				
On 1st day	164.97±17.14	160.97±14.90	95	58	1.929	*P*>0.05 (N/S)
After 1st month	146.00±14.88	133.83±15.34	95	58	6.237	*P*<0.001 (H/S)
After 2nd month	136.97±10.58	109.20±11.86	95	58	19.154	*P*<0.001 (H/S)
After 3rd month	134.73±10.12	95.73±15.06	95	58	23.550	*P*<0.001 (H/S)
After 4th month	134.63±9.74	89.67±16.24	95	58	25.995	*P*<0.001 (H/S)
After 5th month	135.20±9.02	86.97±11.22	95	58	36.695	*P*<0.001 (H/S)
After 6th month	133.67±9.88	85.77±13.52	95	58	31.325	*P*<0.001 (H/S)
After 7th month	134.70±9.82	86.30±13.80	95	58	31.305	*P*<0.001 (H/S)
After 8th month	132.77±7.74	86.80±12.46	95	58	34.348	*P*<0.001 (H/S)
After 9th month	131.70±9.64	81.30±8.48	95	58	42.981	*P*<0.001 (H/S)

FBS: Fasting blood sugar, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom

Table 3: Measurement between Group 1 (control) and Group 2 of HDL parameter

	Group 1 (control) (*N*=30)			Group 2 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	36-44	39.43±2.29	0.417	36-43	39.57±2.14	0.392
After 3rd month	39-46	41.93±1.96	0.359	39-44	42.40±2.04	0.373
After 6th month	40-48	43.47±1.85	0.338	42-46	44.17±1.97	0.359
After 9th month	40-48	43.73±2.03	0.371	42-48	44.90±1.88	0.344

HDL: High density lipoprotein, SD: Standard deviation, SE: Standard error

Table 4: Unpaired *t*-test between Group 1 (control) and Group 2 of HDL parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 2 (*N*=30)				
On 1st day	39.43±4.58	39.57±4.28	95	58	0.245	*P*>0.05 (N/S)
After 3rd month	41.93±3.92	42.40±4.08	95	58	0.910	*P*>0.05 (N/S)
After 6th month	43.47±3.70	44.17±3.94	95	58	1.419	*P*>0.05 (N/S)
After 9th month	43.73±4.06	44.90±3.76	95	58	2.316	*P*<0.01 (S)

HDL: High density lipoprotein, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom, NS: Not significant, S: Significant

Table 5: Measurement between Group 1 (control) and Group 3 of HDL parameter

	Group 1 (control) (*N*=30)			Group 3 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	36-44	39.43±2.29	0.417	36-43	39.70±1.95	0.356
After 3rd month	39-46	41.93±1.96	0.359	39-46	42.67±1.95	0.357
After 6th month	40-48	43.47±1.85	0.338	41-48	45.37±2.21	0.403
After 9th month	40-48	43.73±2.03	0.371	42-49	46.43±2.18	0.397

HDL: High density lipoprotein, SD: Standard deviation, SE: Standard error

Table 6: Unpaired *t*-test between Group 1 (control) and Group 3 of HDL parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 3 (*N*=30)				
On 1st day	39.43±4.58	39.70±3.90	95	58	0.492	*P*>0.05 (N/S)
After 3rd month	41.93±3.92	42.67±3.90	95	58	1.466	*P*>0.05 (N/S)
After 6th month	43.47±3.70	45.37±4.42	95	58	3.611	*P*<0.001 (H/S)
After 9th month	43.73±4.06	46.43±4.36	95	58	4.965	*P*<0.001 (H/S)

HS: Highly significant, NS: Not significant, HDL: High density lipoprotein, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom

Table 7: Measurement between Group 1 (control) and Group 2 of TC parameter

	Group 1 (control) (*N*=30)			Group 2 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	192-224	204.90±22.44	4.097	198-239	217.87±18.67	3.408
After 3rd month	182-216	198.63±9.78	1.785	187-225	201.77±10.06	1.837
After 6th month	172-205	189.13±9.53	1.740	174-210	189.80±9.62	1.755
After 9th month	168-201	185.87±9.37	1.710	170-201	184.37±8.70	1.589

TC: Total cholesterol, SD: Standard deviation, SE: Standard error

Group 3 were 158.37 ± 12.58, 137.50 ± 12.26, and 152.00 ± 15.06, respectively. The mean TG level decreased highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control (Tables 12 and 14).

Table 8: Unpaired *t*-test between Group 1 (control) and Group 2 of TC parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 2 (*N*=30)				
On 1st day	204.90±44.88	217.87±37.34	95	58	2.434	*P*<0.01 (S)
After 3rd month	198.63±19.56	201.77±20.12	95	58	1.226	*P*>0.05 (N/S)
After 6th month	189.13±19.06	189.80±19.24	95	58	0.271	*P*>0.05 (N/S)
After 9th month	185.87±18.74	184.37±17.40	95	58	0.643	*P*>0.05 (N/S)

TC: Total cholesterol, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom, NS: Not significant, S: Significant

Table 9: Measurement between Group 1 (control) and Group 3 of TC parameter

	Group 1 (control) (*N*=30)			Group 3 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	192-224	204.90±22.44	4.097	210-235	219.90±6.76	1.234
After 3rd month	182-216	198.63±9.78	1.785	192-217	201.90±6.83	1.247
After 6th month	172-205	189.13±9.53	1.740	175-197	184.43±7.15	1.306
After 9th month	168-201	185.87±9.37	1.710	168-190	176.37±7.96	1.454

TC: Total cholesterol, SD: Standard deviation, SE: Standard error

Table 10: Unpaired *t*-test between Group 1 (control) and Group 3 of TC parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 3 (*N*=30)				
On 1st day	204.90±44.88	219.90±13.52	95	58	3.506	*P*<0.01 (S)
After 3rd month	198.63±19.56	201.90±13.66	95	58	1.501	*P*>0.05 (N/S)
After 6th month	189.13±19.06	184.43±14.30	95	58	2.161	*P*<0.01 (S)
After 9th month	185.87±18.74	176.37±15.92	95	58	4.232	*P*<0.001 (H/S)

TC: Total cholesterol, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom, HS: Highly significant, NS: Not significant, S: Significant

Table 11: Measurement between Group 1 (control) and Group 2 of TG parameter

	Group 1 (control) (*N*=30)			Group 2 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	160-192	179.70±8.42	1.537	167-195	184.47±7.83	1.429
After3rd month	155-183	170.43±7.25	1.324	157-186	169.73±7.79	1.421
After 6th month	150-173	161.87±7.35	1.342	140-162	157.70±8.43	1.539
After 9th month	144-168	158.37±6.29	1.148	137-153	152.00±7.53	1.374

TG: Triglyceride, SE: Standard error, SD: Standard deviation

Table 12: Unpaired *t*-test between Group 1 (control) and Group 2 of TG parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 2 (*N*=30)				
On 1st day	179.70±16.84	184.47±15.66	95	58	2.272	*P*<0.01 (S)
After 3rd month	170.43±14.50	169.73±15.58	95	58	0.360	*P*>0.05 (N/S)
After 6th month	161.87±14.70	157.70±16.86	95	58	2.042	*P*<0.01 (S)
After 9th month	158.37±12.58	152.00±15.06	95	58	3.556	*P*<0.001 (H/S)

TG: Triglyceride, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom

The LDL levels at day 1 in Group 1, Group 2, and Group 3 were 102.93} 12.14, 110.07} 12.32, and 101.47}16.60, respectively. After 3 months, the mean LDL levels of patients in Group 1 (control), Group 2, and Group 3 were 95.20}

8.92, 101.10} 11.58, and 90.17} 15.58, respectively. The mean LDL level decreased significantly in the Group 2 and Group 3 ($P < 0.01$) as compared to control. After 6 months, the mean LDL levels of patients in Group 1 (control), Group 2 and Group 3 was 89.90} 9.04, 92.93} 11.78 and 84.20} 14.98, respectively. The mean LDL level decreased highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control. After 9 months, the mean LDL levels of patients in Group 1 (control), Group 2, and Group 3 was 84.70} 6.98, 84.13} 11.40 and 78.70} 13.68, respectively. The mean LDL level decreased highly significantly in the Group 2 and Group 3 ($P < 0.001$) as compared to control (Tables 16 and 18).

HDL Parameter

It is protective as it facilitate removal of cholesterol from tissues. It's normal plasma level must be >60 mg/dl.

TC Parameter

It's normal plasma level must be <200 mg/dl. Above this value important risk factor of cardio and cerebro vascular disease.

TG Parameter

It is as important as cholesterol in causing atherogenic diseases. It's plasma level must be <140 mg/dl.

LDL Parameter

It has the least capacity to clear the lipids from plasma. It's normal level must be below 130 mg/dl.

Safety Evaluation

In all groups, 2.22% of patient reported nausea, 1.11% flatulence, 3.33% diarrhea, 1.11% constipation, 2.22% rashes, 4.44% headache, 4.44% abdominal pain, and 3.33% metallic taste.

DISCUSSION

The administration of powder of *B. aristata* at 1.5 and 3 g daily dose as add on therapy in patients of Groups 2 and 3 produced a highly significant reduction in FBS, lipids, and lipoproteins level. The reduction and stabilization of fasting glycemic control ($P < 0.001$) when compared with their respective control were observed from 1 month onward till the end of the study

Table 13: Measurement between Group 1 (control) and Group 3 of TG parameter

	Group 1 (control) (*N*=30)			Group 3 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	160-192	179.70±8.42	1.537	183-205	192.13±5.82	1.062
After 3rd month	155-183	170.43±7.25	1.324	155-181	168.87±5.88	1.074
After 6th month	150-173	161.87±7.35	1.342	133-157	146.27±6.83	1.247
After 9th month	144-168	158.37±6.29	1.148	124-149	137.50±6.13	1.119

TG: Triglyceride, SD: Standard deviation, SE: Standard error

Table 14: Unpaired *t*-test between Group 1 (control) and Group 3 of TG parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 3 (*N*=30)				
On 1st day	179.70±16.84	192.13±11.64	95	58	6.651	*P*<0.001 (H/S)
After 3rd month	170.43±14.50	168.87±11.76	95	58	0.915	*P*>0.05 (N/S)
After 6th month	161.87±14.70	146.27±13.66	95	58	8.516	*P*<0.001 (H/S)
After 9th month	158.37±12.58	137.50±12.26	95	58	13.015	*P*<0.001 (H/S)

TC: Total cholesterol, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom

Table 15: Measurement between Group 1(control) and Group 2 of LDL parameter

	Group 1 (control) (*N*=30)			Group 2 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	94-116	102.93±6.07	1.109	100-122	110.07±6.16	1.124
After 3rd month	86-104	95.20±4.46	0.814	92-112	101.10±5.79	1.057
After 6th month	80-104	89.90±4.52	0.825	82-106	92.93±5.89	1.075
After 9th month	78-92	84.70±3.49	0.636	74-96	84.13±5.70	1.041

LDL: Low density lipoprotein, SD: Standard deviation, SE: Standard error

(Tables 1 and 2). The hypolipidemic effect of *B. aristata* found statistically significant; however, no significant improvement in Group 2 HDL level up to 6th month, but significant improvement was noted at 9th month as compared to the control (P <0.01; Table 3 and 4) while in Group 3 no significant improvement was seen on 3rd month but a highly significant improvement occurred from 6th month onward (P <0.001; Table 5). In Group 2, no significant reduction in TC level was found even after 9 months of therapy but in Group 3 a highly significant reduction was seen from 6th month (P < 0.001; Tables 7 and 9). While in Group 2 TG level, no significant reduction was seen at 3rd month, but after 6th month onward a significant reduction was noted (P < 0.01; Table 11) and then in 9 month a highly significant reduction was seen (P < 0.001; Table 11) but in Group 3 no significant reduction was seen in 3rd month, from 6th month onward a highly significant reduction occurred (P < 0.001; Table 13). In Group 2 and Group 3, a significant reduction in LDL was noted from 3rd month (P < 0.01; Tables 15 and 17) and highly significant reduction was seen from 6th month onward (P < 0.001; Table 15).

Several studies, mostly performed in the Chinese population, have reported the effects of berberine on the lipidic and glycemic profile,[18,19] but very few have reported the effect of berberine in Caucasians.[20-22] Conventional hypoglycemic drugs may produced only suboptimal control in blood sugar and lipid levels or unacceptable adverse effect. 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 *B. aristata* DC on Type 2 DM patients as add on thearapy. *B. aristata* contains protoberberine and bisisoquinoline type of alkaloid. Root of plant *B. aristata* contains alkaloid which are berbamine, berberine, oxycanthine, epiberberine, palmatine, dehydrocaroline, jatrorhizine and columbamine karachine, taximaline, oxyberberine, dihyrokarachine, and aromoline. Four alkaloids, pakistanine, and methylpakistanine, pseudopalmatine chloride pseudoberberine chloride were also isolated from *B. aristata*. Asecobisbenzl isoquinoline or simple isoquinoline alkaloid was isolated from *B. aristata*. The major alkaloid found in *B. aristata* is berberine having yield of 2.23% followed by palamatine.[23] The antihyperglycemic 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 Yin et al. reported Berberine regulates glucose metabolism through multiple mechanisms of action: (1) Stimulation of glucose uptake by

Table 16: Unpaired *t*-test between Group 1 (control) and Group 2 of LDL parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 2 (*N*=30)				
On 1st day	102.93±12.14	110.07±12.32	95	58	0.467	*P*>0.05 (N/S)
After 3rd month	95.20±8.92	101.10±11.58	95	58	2.235	*P*<0.01 (S)
After 6th month	89.90±9.04	92.93±11.78	95	58	4.422	*P*<0.001 (H/S)
After 9th month	84.70±6.98	84.13±11.40	95	58	4.522	*P*<0.001 (H/S)

LDL: Low density lipoprotein, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom

Table 17: Measurement between Group 1 (control) and Group 3 of LDL parameter

	Group 1 (control) (*N*=30)			Group 3 (*N*=30)		
	Range	Mean±SD	SE	Range	Mean±SD	SE
On 1st day	94-116	102.93±6.07	1.109	96-118	101.47±8.30	1.516
After 3rd month	86-104	95.20±4.46	0.814	88-106	90.17±7.79	1.422
After 6th month	80-104	89.90±4.52	0.825	81-105	84.20±7.49	1.369
After 9th month	78-92	84.70±3.49	0.636	76-94	78.70±6.84	1.249

LDL: Low density lipoprotein, SD: Standard deviation, SE: Standard error

Table 18: Unpaired *t*-test between group 1 (control) and group 3 of LDL parameter

	Mean±2SD		CI %	df	Calculated *t*-value	*P* value
	Group 1 (control) (*N*=30)	Group 3 (*N*=30)				
On 1st day	102.93±12.14	101.47±16.60	95	58	0.778	*P*>0.05 (N/S)
After 3rd month	95.20±8.92	90.17±15.58	95	58	3.086	*P*<0.01 (S)
After 6th month	89.90±9.04	84.20±14.98	95	58	3.566	*P*<0.001 (H/S)
After 9th month	84.70±6.98	78.70±13.68	95	58	4.280	*P*<0.001 (H/S)

HS: Highly significant, NS: Not significant, S: Significant, LDL: Low density lipoprotein, SD: Standard deviation, CI: Confidence interval, df: Degree of freedom

glucose transporter type 4 upregulation, (2) activation of 5′ adenosine monophosphate-activated protein kinase (AMPK), as a consequence of the inhibition of mitochondrial function, (3) suppression of adipogenesis, by inhibiting peroxisome proliferator-activated receptor gamma and C-enhancer-binding protein alpha function, (4) stimulation of glucagon-like peptide-1 release from ileal cells, (5) suppression of human protein tyrosine phosphatase 1B, (6) stimulation of the pancreatic G protein-coupled receptor 40, and (7) reduction of intestinal glucose absorption, by inhibiting α-glucosidase activity.[18] 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 DM. *B. aristata* has antioxidant property, this appears to be a reflection of reduced oxidative stress. In DM 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, and glutathione reductase activity.[25] Patients of DM frequently have dyslipidemia which can be attributed to hyperglycemia and its attendant oxidative stress induced alteration in synthesis and metabolism of lipoproteins. A large body of evidence indicate that incidence of hyperlipidemia and its complication are growing in the world. Hyperlipidemia develops the risk of many diseases such as coronary heart disease, atherosclerosis, hypertenstion and Type 2 DM. The hypolipidemic effect of *B. aristata* may be due to the presence of berberine alkaloids. In previous studies, berberine is introduced as lipid-lowering therapeutic agent. It is reported that berberine down-regulated the expression of genes involved in lipogenesis and up-regulated those involved in energy expenditure in adipose and muscle tissues such as glycerol kinase and acyl-CoA dehydrogenase. Furthermore, this lipid-lowering effect of berberine has been reported by other investigators which shows that BBR can reduce metabolic disorders, including obesity, insulin resistance and hyperlipidemia by stimulating AMPK activity in both *in vivo* and *ex vivo* experiments.[26] Kong et al. have also reported that berberine upregulates LDL-receptor expression independent of sterol regulatory element-binding proteins but dependent on extracellular signal-regulated kinase and c-junction N-terminal kinase) activation, which results in TC and LDL-C reduction (by about 30% and 25%, respectively). This upregulation occurs through a posttranscriptional mechanism that stabilizes messenger ribonucleic acid, making berberine a cholesterol-lowering drug endowed properties, berberine also reduces TGs by about 35%. These actions on the lipid profile with a different mechanism of action from that of statins.[27] Along with its cholesterol-lowering have been observed in both animals and humans.[28] Upwar et al. showed the potential of *B. aristata* in significantly controlling the diabetes induced hyperlipidemia. The levels of TC and TGs were raised in diabetic rats after 30 days of study when compared with normal control group. The levels of TC and TGs were controlled significantly in the groups treated with 50 and 100 mg/kg body weight dose of the ethanol extract when compared with diabetic control.[29] Recently, the inhibitory effect of berberine has been reported on the liver phosphatidate phosphohydrolase (PAP) activity. catalyzes the dephosphorylation of phosphatidic acid to form inorganic phosphate and 1,2 diacylglycerol productions.[30,31] In liver tissue, PAP is an important key regulatory enzyme in lipid metabolism pathway especially triacylglycerol and glycerophospholipids. The produced diacylglycerol from phosphatidic acid serves as a precursor for synthesis of TG and other phospholipids. In organism, TG is a critical storage molecule for periods of food deprivations. In human, the regulation of TG storage is very important because both excessive and inadequate fat storage are accompanied with dyslipidemia, insulin resistance, and diabetes. Therefore, any alteration in PAP activity can influence lipid metabolism in the body.[32] Farvid et al. suggested that supplementation of antioxidants and trace-elements contribute to increase in HDL and decrease in LDL levels in diabetes patients. As berberine has antioxidant property so may be responsible for its hypolipidemic effect.[33]

It is significant to note that the *B. aristata* as add on therapy exhibited no major or life threatening adverse effect in our study. Minor side effects such as nausea, flatulence, diarrhea, constipation, rashes, headache, abdominal pain, metallic taste, anorexia, and weight gain are quite tolerable and pose no chance of withdrawl of this therapy in the light of significant therapeutic benefits observed. *B. aristata* add on therapy thus provided better glycemic and lipidemic control and was found to exhibit beneficial effects in preventing Type 2 DM. In our study, there were only measuring of FBS to screen the patients of Type 2 DM, and there is no data collected about postprandial sugar level so we cannot predict about its effect on postprandial hyperglycemia. Thus, further study required to determine the definite role in DM.

CONCLUSION

On the basis of our study administration of *B. aristata* (stem powder) as add on therapy is effective in improving glycemic control as well as lipid profile with no major adverse effects in Type 2 DM. Thus, the use of *B. aristata* as an add on therapy could represent a good treatment option before increasing oral antidiabetic and antihyperlipidemic dose or initiating insulin and hypolipidec therapy in Type 2 diabetic patients with suboptimal glycemic and lipidemic control to avoid unwanted adverse effects and may cut down cost of treatment.

REFERENCES

1. Areekal B, Collins AJ, Foley RN, Chavers B. Prevalance of risk factors for cardiovascular disease among adults older than

30 years in a rural area in central Kerala, India. Int J Med Sci Public Health. 2015;4(12):1655-9.
2. Goldberge AC. Dyslipidemia. Available from: https://www.msdmanuals.com. [Last accessed on 2017 Dec 15].
3. Murty R, Anand P, Murali YK, Tandon V. *In vitro* evaluation of anti-diabetic activity of aqueous and ethanoic leaves extracts of *Chloroxylon swietenia*. Natl J Phys Pharm Pharmacol. 2017;7(5):486-9.
4. Tripathi KD. Insulin, Oral Hypoglycemic Drugs and Glucagon: Essential of Medical Pharmacology. 7th ed. New Delhi: Medical Publishers (P) Ltd; 2013. p. 258.
5. Sukandar EY, Permana H, Adnyana IK, Sigit JI, Ilyas RA, Hasimun P, et al. Clinical study of turmeric (*Curcuma longa* L.) and garlic (*Allium sativum* L.) extracts as anti-hyperglycemic and anti-hyperlipidemia agent in Type-2 diabetes-dyslipidemia patients. Int J Pharmacol. 2010;6(4):456-63.
6. Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. Harrison's Principle on Internal Medicine. 15th ed. New York: McGraw Hill Medical; 2001.
7. Chakrabarti R, Bhavtaran S, Narendra P, Varghese N. Dipeptidyl peptidase-IV inhibitory activity of *Berberis aristata*. J Nat Prod. 2011;4:158-63.
8. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414:782-7.
9. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections. Diabetes Care. 1998;21(9):1414-31.
10. Boyko EJ, de Courten M, Zimmet PZ, Chitson P, Tuomilehto J, Alberti KG. Features of the metabolic syndrome predict higher risk of diabetes and impaired glucose tolerance: A prospective study in Mauritius. Diabetes Care. 2000;23(9):1242-8.
11. Ramachandran A, Snehalatha C, Latha E, Vijay V, Viswanathan M. Rising prevalence of NIDDM in an urban population in India. Diabetologia. 1997;40(2):232-7.
12. 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):2457-71.
13. Li WL, Zheng HC, Bukuru J, de Kimpe N. Natural medicines used the traditional Chinese medical system for therapy of diabetes mellitus. J Ethnopharmacol. 2004;92(1):1-21.
14. Lopes-Virella MF, Stone P, Ellis S, Colwell JA. Cholesterol determination in high-density lipoproteins separated by three different methods. Clin Chem. 1977;23(5):882-4.
15. Allain CC, Poon LS , Chan CS , Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem. 1974;20(4):470-5.
16. Bablok W, Passing H, Bender R, Schneider B. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem. 1988;26(3):783-90.
17. Nauck M, Warnick GR, Rifai N. Methods for measurement of LDL-cholesterol: A critical assessment of direct measurement by homogeneous assays versus calculation. Clin Chem. 2002;48(2):236-54.
18. 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;2012:591654.
19. 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):1113-24.
20. 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;5:213-7.
21. Orio F, Muscogiuri G, Palomba S, Savastano S, Volpe A. Bebeerine improves reproductive features in obese Caucasian women with polycystic ovary syndrome independently of changes of insulin sensitivity. Eur J Clin Nutr. 2013;8(5):e200-4.
22. Mohammad YM. Clinical evaluation of antidiabetic activity of *Trigonella* seeds and *Aegle marmelos* leaves. World Appl Sci J. 2009;7(10):1231-4.
23. Department of Ayurveda. The Ayurveda Pharmacopoeia of India. Vol. 1. New Delhi: Government of India, Ministry of Health and Family Welfare Department of AYUSH; 2007. p. 34-6.
24. Paolisso G, Gambardella A, Tagliamonte MR, Saccomanno F, Salvatore T, Gualdiero P, et al. Does free fatty acid infusion impair insulin action also through an increase in oxidative stress? J Clin Endocrinol Metab. 1996;81(12):4244-8.
25. Singh J, Kakkar P. Antihyperglycemic and antioxidant effect of *Berberis aristata* root extract and its role in regulating carbohydrate metabolism in diabetic rats. J Ethnopharmacol. 2009;123(1):22-6.
26. Heidarian E, Rafieian-Kopaei M, Khoshdel A. Metabolic effects of berberine on liver phosphatidate phosphohydrolase in rats fed on high lipogenic diet: An additional mechanism for hypolipemic effects of berberine. Asian Pac J Trop Biomed. 2014;4:S429-35.
27. Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med. 2004;10(12):1344-51.
28. Hu Y, Davies GE. Berberine inhibits adipogenesis in high-fat diet-induced obesity mice. Fitoterapia. 2010;81(5):358-66.
29. Upwar NK, Patel R, Waseem N, Mahobia NK. Hypoglycemic effect of methanol extract of *Berberis aristata* D.C stem on normal and streptozotocin induced diabetic rats. Int J Pharm Pharm Sci. 2011;3(1):222-4.
30. Carman GM, Han GS. Roles of phosphatidate phosphatase enzymes in lipid metabolism. Trends Biochem Sci. 2006;31(12):694-9.
31. Heidarian E, Haghighi B. Enzymological characteristic of plasma membrane phosphatidate phosphohydrolase (PAP_2) from rat liver. Iran J Sci Technol A Sci. 2008;32:117-27.
32. Wang Q, Zhang M, Liang B, Shirwany N, Zhu Y, Zou MH. Activation of AMP-activated protein kinase is required for berberine-induced reduction of atherosclerosis in mice: The role of uncoupling protein 2. PLoS One. 2011;6(9):e25436.
33. Farvid MS, Siassi F, Jalali M, Hosseini M, Saadat N. The impact of vitamin or mineral supplementation on lipid profile in Type-2 DM. Diabetes Res Clin Pract. 2004;23:272-9.

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