Journal of Food and Nutrition Research, 2020, Vol. 8, No. 4, 212-215
Available online at http://pubs.sciepub.com/jfnr/8/4/8
Published by Science and Education Publishing
DOI:10.12691/jfnr-8-4-8

Efficacy of Berberis aristata Compared to Metformin in Improving Glycemic Control and Insulin Resistance in Patients with Type 2 Diabetes Mellitus

Giuseppe Derosa[1,2,*], Giovanni Gaudio[3], Angela D'Angelo[1,2], Pamela Maffioli[1]

[1]Department of Internal Medicine and Therapeutics, University of Pavia, PAVIA, Italy
[2]Laboratory of Molecular Medicine, University of Pavia, PAVIA, Italy
[3]Internal Medicine Division, Ospedale Angelo Bellini, Somma Lombardo, VARESE, Italy
*Corresponding author: giuseppe.derosa@unipv.it

Received April 25, 2020; Revised May 27, 2020; Accepted June 03, 2020

Abstract **Aim:** the study was aimed to evaluate the action of a combination of an extract of *Berberis aristata*/*Silybum marianum* compared to metformin in a sample of Caucasian type 2 diabetic patients not taking anti-diabetic drugs. **Methods:** we enrolled 109 type 2 diabetic patients and randomized them to take *Berberis aristata*/*Silybum marianum 588/108* mg or metformin for 6 months, in a double-blind, randomized, controlled, clinical trial. **Results:** glycated hemoglobin was similarly reduced by both *Berberis aristata*/*Silybum marianum* and metformin ($p < 0.05$ vs baseline, for both treatments), without significant differences between the two treatments. The same trend was recorded for FPG ($p < 0.05$ vs baseline, for both treatments), and PPG ($p < 0.01$ vs baseline, for both treatments). Both treatment reduced FPI and HOMA-IR ($p < 0.05$ vs baseline), without any differences between the two arms. Both *Berberis aristata*/*Silybum marianum* and metformin improved TC, LDL-C and Tg compared to baseline ($p < 0.05$ for both); however, *Berberis aristata/Silybum marianum* better improved these parameters compared to metformin ($p < 0.05$ for all). **Conclusions:** *Berberis aristata/Silybum marianum* can be a valid alternative to metformin in patients not well controlled by diet.

Keywords: *Berberis aristata/Silybum marianum, glycemic control, metformin*

Cite This Article: Giuseppe Derosa, Angela D'Angelo, and Pamela Maffioli, "Efficacy of Berberis aristata Compared to Metformin in Improving Glycemic Control and Insulin Resistance in Patients with Type 2 Diabetes Mellitus." *Journal of Food and Nutrition Research*, vol. 8, no. 4 (2020): 212-215. doi: 10.12691/jfnr-8-4-8.

1. Introduction

Type 2 diabetes mellitus is one of the most impacting illness of the human race implicated with many clinical manifestations. The prevalence of type 2 diabetes is spreading worldwide, with a heavy economic on health care expenditure [1]. Type 2 diabetes mellitus is characterized by an absolute or relative deficiency of insulin, leading to hyperglycemia. According to World Health Organization projections, people with diabetes will increase to 300 million or more by 2025 [2].

In the recent years, several anti-diabetic agents have been marketed, however, researchers are still searching for an ideal drug acting as both a hypoglycemic agent and to reduce diabetes-related complications. Several studies conducted both in animal and human, showed the efficacy of Berberine, an isoquinoline alkaloid extract, as a hypoglycemic agent.

Berberis aristata is an Indian medicinal plant, belonging to the family *Berberidaceae*; it also called *Indian berberi, Daruharidra, Daruhaldi, Darvi and Chitra*. Mechanistic studies have revealed beneficial effects of *Berberis aristata* on diabetes-related complications. *Berberis aristata* can be a potential candidate drug to treat type 2 diabetes. *Berberis aristata*, anyway, is rather defective in terms of oral bioavailability [3], affected by a gut extrusion process P-glycoprotein (P-gp) mediated [4]. In literature is reported a not-controlled pilot study about the addition of a combination of *Berberis aristata* extract and *Silybum marianum* to previously taken oral type 2 diabetic agents for patients with suboptimal glycemic control. This trial demonstrated the usefulness of the add-on therapy performed with such a nutraceutical combination [5]. A review published by Chang et al., confirmed these positive effects [6].

In literature, several studies have been published about the benefits of *Berberis aristata* on dysglycemia and insulin resistance [7,8]; however, randomized, clinical trials, about the effects of *Berberis aristata* in type 2 diabetic patients, are lacking.

All data considering, we conducted a study aimed to evaluate the effects of a combination of *Berberis aristata*/*Silybum marianum* extract compared to metformin in a sample of Caucasian type 2 diabetic patients naïve to anti-diabetic treatment.

2. Materials and Methods

2.1. Study Design

We conducted this 6-months, double-blind, randomized, controlled, clinical trial at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy).

The study protocol was approved by the institutional review board and was conducted in accordance with the 1994 Declaration of Helsinki, and its amendments and the Code of Good Clinical Practice [9]. All patients had to provide written informed consent before be enrolled in this study after a full explanation of the procedures had been given.

2.2. Patients

We enrolled 109 Caucasian patients with type 2 diabetes mellitus aged >18 of either sex (Table 1) according to the ESC (European Society of Cardiology) and the EASD (European Association for the Study of Diabetes) Guidelines criteria [10], naïve to treatment, and with glycated hemoglobin (HbA_{1c}) level ≥ 6.5 %, and in overweight (BMI≥ 25, and < 30 Kg/m^2).

Patients with previous ketoacidosis or unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded. Impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or severe anemia were considered exclusion criteria. Patients affected by serious cardiovascular disease (CVD) (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment were also excluded. Pregnant or breastfeeding women or women of childbearing potential were also excluded, if not taking adequate contraceptive precautions.

Investigators contacted suitable patients, identified from review of case notes and/or computerized clinic registers, in person or by phone.

2.3. Diet and Physical Activity

At baseline, all patients were already following an adequate diet, and were encouraged to maintain their usual physical activity. The controlled-energy diet (~600 kcal daily deficit) followed National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) recommendations [11]. 50% of calories derived from carbohydrates, 30% from fat (< 7% saturated, up to 10% polyunsaturated, and up to 20% monounsaturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/d, and35 g/d of fiber. Patients were followed by a dietitian and/or specialist physician.

2.4. Treatment

At baseline, patients were divided into two groups according to baseline HbA_{1c} value:

- Patients with HbA_{1c} ≥ 6.5% and < 7.5%, received *Berberis aristata*/*Silybum marianum 588/108* mg, one tablet twice a day, or metformin 500 mg, twice a day, after main meal for 6 months;
- Patients with HbA_{1c} ≥ 7.5% and ≤ 8.5% were treated with *Berberis aristata*/*Silybum marianum 588/108* mg, one tablet three times a day, or metformin 500 mg three times a day after main meals for 6 months.

Both treatments were identical, opaque, tablets in coded bottles to ensure the blind status of the study. Randomization was granted using a drawing of envelopes containing randomization codes prepared by a statistician. Medication compliance was assessed by counting the number of tablets returned at the time of specified clinic visits. All medications were provided free of charge.

2.5. Assessments

At the study start, we collected medical history, physical examination, vital signs (blood pressure and heart rate), a 12-lead electrocardiogram, measurements of height and body weight, calculation of body mass index (BMI), abdominal circumference (Abd. Cir.), assessment of fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), HbA_{1c}, fasting plasma insulin (FPI), homeostatic model assessment for insulin resistance (HOMA-IR), lipid profile. Anthropometric and metabolic parameters were evaluated at baseline, and after 6 months.

For a description of how various parameters were evaluated, see our previous publications [7,8].

2.6. Statistical Analysis

We conducted an intention-to-treat (ITT) analysis in patients receiving ≥ 1 dose of study medication, and a the tolerability analysis in patients receiving ≥ 1 dose of trial medication after randomization. ANCOVA was used to assess statistical significance of the independent effects of treatments on various variables. We chose a 1-sample *t* test to compare values obtained before and after treatment administration, and a 2-sample *t* test for between-group comparisons. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean (SD) [12]. For all statistical analyses, we considered $p< 0.05$ as statistically significant.

3. Results

3.1. Study Sample

A total of 109 patients were enrolled in the trial, 57 were randomised to *Berberis aristata*/*Silybum marianum* and 52 to metformin; of these, 104 completed the trial. Concomitant diseases and medications of all the patients are listed in Table 1.

Table 1. Concomitant diseases and medications of all the patients

	Berberis aristata/Silybum marianum	Metformin
Concomitant disease, n (%)	57 (100)	52 (100)
Hypertension	44 (77.2)	40 (76.9)
Hypercholesterolemia	31 (54.4)	26 (50.0)
CHD	3 (5.3)	2 (3.8)
Stroke	1 (1.7)	0 (0)
Hyperuricemia	8 (17.8)	10 (19.2)
Concurrent medications, n (%)	57 (100)	52 (100)
ACE-I	28 (49.1)	30 (57.7)
ARBs	29 (50.9)	22 (42.3)
β-blockers	7 (12.3)	4 (7.7)
α-blockers	5 (8.8)	7 (13.5)
Diuretics	10 (17.5)	9 (17.3)
Statins	21 (36.8)	18 (34.6)
Ezetimibe	3 (5.3)	1 (1.9)
Fibrates	1 (1.8)	1 (1.9)
Omega-3	4 (7.0)	2 (3.8)
Acetylsalicylic acid	4 (7.0)	2 (3.8)
Allopurinol	6 (10.5)	7 (13.5)
Febuxostat	2 (3.5)	3 (5.8)

Data are expressed as means ± SD or n and %
CHD: coronary heart disease; ACE-I: angiotensin-converting enzyme-inhibitors; ARBs: angiotensin II receptor blockers.

Table 2. Characteristic of the patients during the study

Parameters	Berberis aristata / Silybum marianum		Metformin	
	Baseline	6 months	Baseline	6 months
N	57	55	52	49
M/F	28/29	27/28	27/25	26/23
Diabetes Duration (years)	1.0 ± 0.3	-	1.2 ± 0.4	-
Smoking status (M/F)	9/11	9/10	8/7	8/7
Weight (Kg)	78.3 ± 7.4	76.1 ± 6.5	76.5 ± 6.8	74.4 ± 6.1
Height (m)	1.69 ± 0.08	-	1.68 ± 0.07	-
BMI (Kg/m^2)	27.4 ± 1.8	26.6 ± 1.3	27.1 ± 1.6	26.4 ± 1.2
AC (cm)	91.7 ± 3.9	90.2 ± 3.6	92.1 ± 4.3	91.3 ± 3.7
HbA_{1c} (%)	7.6 ± 0.8	7.1 ± 0.4*	7.5 ± 0.7	6.9 ± 0.3*
HbA_{1c} (6.5-7.4 %) (%)	48	54	51	58
HbA_{1c} (7.5-8.5 %) (%)	52	46	49	42
FPG (mg/dl)	139.6 ± 10.2	131.1 ± 8.3*	137.4 ± 9.5	127.6 ± 7.4*
PPG (mg/dl)	152.9 ± 16.8	140.7 ± 12.1^	155.2 ± 17.2	138.9 ± 11.3^
FPI (mU/ml)	14.8 ± 6.3	11.5 ± 5.2*	15.2 ± 6.6	11.9 ± 5.4*
HOMA-IR	5.1 ± 2.6	3.8 ± 1.7*	5.2 ± 2.7	3.8 ± 1.6*
TC (mg/dl)	196.4 ± 22.8	161.3 ± 15.7^°	198.1 ± 24.3	183.4 ± 19.2*
LDL-C (mg/dl)	123.3 ± 13.5	90.4 ± 10.3^°	122.5 ± 12.8	109.2 ± 11.7*
HDL-C (mg/dl)	42.7 ± 6.4	44.1 ± 7.1	43.9 ± 6.8	44.5 ± 7.3
Tg (mg/dl)	152.2 ± 37.8	133.8 ± 31.5^°	158.5 ± 40.1	148.3 ± 36.2*

Data are expressed as mean ± standard deviations
*p< 0.05 vs Baseline; ^p< 0.01 vs Baseline; °p< 0.05 vs Metformin
M: males; F: females; BMI: body mass index; AC: abdominal circumference; HbA_{1c}: glycated hemoglobin; FPG: fasting plasma glucose; PPG: post-prandial plasma glucose; FPI: fasting plasma insulin; HOMA-IR: homeostatic model assessment for insulin resistance; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides.

3.2. Anthropometric Parameters

No variation of anthropometric parameters was recorded in neither group (Table 2).

3.3. Glyco-metabolic control and insulin resistance

Glycated hemoglobin was similarly reduced by both *Berberis aristata*/*Silybum marianum* and metformin ($p < 0.05$ vs baseline, for both treatments), without significant differences between the two treatments. The same trend was recorded for FPG ($p < 0.05$ vs baseline, for both treatments), and PPG ($p < 0.01$ vs baseline, for both treatments). Both treatment reduced FPI and HOMA-IR ($p < 0.05$ vs baseline), without any differences between the two treatments (Table 2).

3.4. Lipid Profile

Both *Berberis aristata*/*Silybum marianum* and metformin improved total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and triglycerides (Tg) compared to

baseline ($p < 0.05$ for both); however, *Berberis aristata/Silybum marianum* better improved these parameters compared to metformin ($p < 0.05$ for all). No change was observed in high density lipoprotein-cholesterol (HDL-C) (Table 2).

4. Discussion

Our study showed that *Berberis aristata/Silybum marianum* could be a valid alternative to metformin in patients not well controlled by diet. *Berberis aristata/Silybum marianum* has also the benefit of not giving intestinal adverse events, differently from metformin. Our results are in line with what previously published by Di Pierro et al, [5] they reported a HbA_{1c} reduction of about 0.9%, in line with a reduction of 0.5% reported in our trial. At a first sight, a reader can argue of a less effect of *Berberis aristata/Silybum marianum* in our study, but we have to remember that in our study *Berberis aristata/Silybum marianum* was used as monotherapy, in the study by Di Pierro et al., it was used in addition to previous anti-diabetic treatments [5]. Regarding the mechanisms through which *Berberis aristata/Silybum marianum* lower glycemia, berberine regulates glucose metabolism via multiple mechanisms of action. Berberine enhances glucose uptake by glucose transporter type 4 up modulation, it activates 5-AMP-activated protein kinase as a consequence of inhibition of mitochondrial function, suppresses adipogenesis by inhibition of peroxisome proliferator-activated receptor gamma and C-enhancer-binding protein alpha function, and decreases intestinal glucose absorption inhibiting alpha glucosidase [13].

Moreover, compared to metformin, *Berberis aristata/Silybum marianum* was more effective in improving lipid profile, in line with what already reported by our groups in some previous papers [7,8].

5. Conclusions

Our study showed that *Berberis aristata/Silybum marianum* can be a valid alternative to metformin in type 2 diabetic patients not well controlled by diet. *Berberis aristata/Silybum marianum* has also the benefit of not giving intestinal adverse events, differently from metformin.

References

[1] Shamseddeen, H., Getty, J.Z., Hamdallah, I.N., Ali, M.R., "Epidemiology and economic impact of obesity and type 2 diabetes", *Surg Clin North Am*, 91(6). 1163-1172. Dec.2011.

[2] Tielmans, A., Laloi-Michelin, M., Coupaye, M., Virally, M., Meas, T., Guillausseau, P., "Traitement médicamenteux du diabète de type 2 (première partie)" *Presse Med* 2007; 36: 269-278.

[3] Chen, W. Miao, Y.Q., Fan, D.J., Yang, S.S., Lin, X., Meng, L.K., Tang, X., "Bioavailability study of berberine and the enhancing effects of TPGS on intestinal absorption in rats", *AAPS PharmSciTech*, 12(2). 705-711. Jun.2011.

[4] Pan, G.Y., Wang, G.J., Liu, X.D., Fawcett, J.P., Xie, Y.Y., "The involvement of P-glycoprotein in berberine absorption", *Pharmacol Toxicol*, 91(4). 193-197. Oct.2002.

[5] 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*, 5, 213-217. Jul.2012.

[6] Chang, W., Chen, L., Hatch, G.M., "Berberine as a therapy for type 2 diabetes and its complications: From mechanism of action to clinical studies", *Biochem Cell Biol*, 93(5). 479-486. Oct.2015.

[7] Derosa, G., Bonaventura, A., Bianchi, L., Romano, D., D' Angelo, A., Fogari, E., Maffioli, P., "Effects of Berberis aristata/Silybum marianum association on metabolic parameters and adipocytokines in overweight dyslipidemic patients", *J Biol Regul Homeost Agents*, 27(3). 717-728. Jul-Sep.2013.

[8] Derosa, G., Bonaventura, A., Bianchi, L., Romano, D., D'Angelo, A., Fogari, E., Maffioli, P., "Berberis aristata/Silybum marianum fixed combination on lipid profile and insulin secretion in dyslipidemic patients", *Expert Opin Biol Ther*, 13(11). 1495-1506. Nov.2013.

[9] The Council for International Organisation of Medical Sciences., "Proposed International Guidelines for Biomedical Research Involving Human Subjects", Geneva, 1982.

[10] Rydén, L., Standl, E., Bartnik, M., Van den Berghe, G., Betteridge, J., de Boer, M.J., Cosentino, F., Jönsson, B., Laakso, M., Malmberg, K., Priori, S., Ostergren, J., Tuomilehto, J., Thrainsdottir, I., Vanhorebeek, I., Stramba-Badiale, M., Lindgren, P., Qiao, Q., Priori, S.G., Blanc, J.J., Budaj, A., Camm, J., Dean, V., Deckers, J., Dickstein, K., Lekakis, J., McGregor, K., Metra, M., Morais, J., Osterspey, A., Tamargo, J., Zamorano, J.L., Deckers, J.W., Bertrand, M., Charbonnel, B., Erdmann, E., Ferrannini, E., Flyvbjerg, A., Gohlke, H., Juanatey, J.R., Graham, I., Monteiro, P.F., Parhofer, K., Pyörälä, K., Raz, I., Schernthaner, G., Volpe, M., Wood, D.; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD), "Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD)", *Eur Heart J*, 28(1). 88-136. Jan.2007.

[11] Lichtenstein, A.H., Appel, L.J., Brands, M., Carnethon, M., Daniels, S., Franch, H.A., Franklin, B., Kris-Etherton, P., Harris, W.S., Howard, B., Karanja, N., Lefevre, M., Rudel, L., Sacks, F., Van Horn, L., Winston, M., Wylie-Rosett, J., "Summary of American Heart Association Diet and Lifestyle Recommendations Revision 2006", *Arterioscler Thromb Vasc Biol*, 26. 2186-2191. Oct.2006.

[12] Winer, B.J., "Statistical Principles in Experimental Design", 2nd ed., McGraw-Hill, New York (USA), 1971.

[13] Yin, J., Zhang, H., Ye, J., "Traditional Chinese medicine in treatment of metabolic syndrome", *Endocr Metab Immune Disord Drug Targets*, 8(2), 99-111. Jun.2008.