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LETTER TO THE EDITOR

BIOIMPEDANCE ANALYSIS, METABOLIC EFFECTS AND SAFETY OF THE ASSOCIATION *BERBERIS ARISTATA*/*SILYBUM MARIANUM*: A 52-WEEK DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY IN OBESE PATIENTS WITH TYPE 2 DIABETES

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Berberine, a quaternary isoquinoline alkaloid present in *Berberis aristata*, is well known in terms of cholesterol-lowering, hypoglycemic, and insulin sensitizing effects. Because of its low oral bioavailability, to improve intestinal absorption it has been recently combined with silymarin (*Silybum marianum*). The aim of our placebo controlled study was to evaluate the effects of its association with silymarin on abdominal fat in overweight/obese patients with type 2 diabetes mellitus (T2DM). To do so, 136 obese subjects with T2DM and metabolic syndrome were analyzed for fasting blood glucose and insulin, Insulin Resistance index according to the Homeostatic Model Assessment (HOMA-R), total, HDL and LDL cholesterol, triglycerides, uric acid, BMI, waist circumference, waist to hip ratio and underwent bioelectrical impedance to assess % abdominal fat. All the above-mentioned parameters, as recorded at enrollment, after 6 months and at the end of the study, had significantly improved in the BBR-treated group in respect to baseline and to the control group. A validated national cardiovascular risk score also improved significantly after BBR treatment in respect to placebo. Our results point to a clinically significant effect in obese people with T2DM and metabolic syndrome. Moreover, for the first time, they provide evidence of a significant uric acid lowering activity as an additive beneficial effect of the association BBR + silymarin.

To the Editor,

Suboptimal glycemic control is a common situation in diabetes, regardless of the wide range of drugs available to reach glycemic targets. Moreover, the side effects of many hypoglycemic drugs are often the reason behind frequently observed poor treatment adherence (1).

Conversely, Chinese herbal medicine (CHM), has been used for more than 3,000 years and is widely resorted to in East Asia (2). In Western countries there is a growing interest in the role of CHM in managing metabolic disorders and insulin resistance-related diseases, including resistant hypertension (3).

Berberine (BBR), an isoquinoline alkaloid of the protoberberine type identified in an array of plants, has been used in Indian and Chinese medicine for a long time. It has been found in *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (the Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric). BBR and its extracts have been attributed significant antimicrobial activity

Key words: Berberine-silymarin, nutraceutical, T2DM, metabolic syndrome, body composition, Bioimpedance.

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

against a variety of organisms, including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. BBR has proved to be effective against bacterial diarrhea and intestinal parasite infections and this explains why at a high dosage constipation has been reported as a possible side effect (4).

More recently, clinical research on BBR has revealed novel pharmacological properties and multiple therapeutic applications, mainly concerning hypercholesterolemia, hypertrygliceridemia and diabetes (5, 6).

In fact, BBR significantly decreases glycosylated hemoglobin (HbA1c), fasting blood glucose, and postprandial blood glucose with an effect similar to that of metformin, even if it likely acts via a different mechanism (7, 8). In addition, some meta-analyses provided evidence of the efficacy of BBR against diabetes mellitus (27 trials with competitors as metformin, phenformin, glipizide, rosiglitazone and other oral hypoglycaemic agents), hyperlipidemia (six trials *vs* simvastatin and atorvastatin as lipid-lowering drugs), obesity, and even "treatment resistant" arterial hypertension (4 trials *vs* nitrendipine, amlodipine and metoprolol as blood pressure lowering drugs) (9).

Due to its poor oral bioavailability, BBR from *Berberis aristata* has been combined with silymarin (*Silybum marianum* extract) which - besides having a fully recognized favorable effect on the liver based on cell membrane stabilization, protein synthesis stimulation and organ protection from intracellular free radicals and lipid peroxidation through enhanced superoxide dismutase and glutathione peroxidase activities - is rich in flavolignanes (60–80%) and optimizes gut BBR absorption (10).

Another item of interest is the frequent association between high circulating levels of uric acid and metabolic diseases, such as diabetes mellitus, dyslipidemia, arterial hypertension and the metabolic syndrome, and especially as a major reversible risk factor for metabolic and cardiovascular diseases (11).

Based on this large body of evidence, with special reference to enhanced adipose and muscle cell glucose utilization, we undertook a 52-week placebo-controlled study on a BBR–silymarin association having as primary endpoint the extent and distribution of fat tissue in a large group of obese subjects with T2DM kept on a low-calorie diet.

Secondary endpoints were: (i) anthropometric and biochemical parameters; (ii) blood pressure levels; (iii) uric acid levels; (iv) BBR safety, tolerability, and drop out rate; and (v) durability of BBR effects.

MATERIALS AND METHODS

Patients, diet, and measures

This was a double-blind, placebo-controlled study conducted in accordance with the Helsinki Declaration. The study was formally approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli". One hundred thirty-six patients with T2DM gave their informed consent and were enrolled in the study.

Inclusion criteria were: age between 18 and 70 years; obesity (body mass index (BMI) >30 kg/m^2); altered glucose profile (fasting blood glucose ≥126 mg/dl and insulin resistance index (HOMA-R) >2.5); altered lipid profile (total cholesterol >220 mg/dl; LDL-cholesterol >100 mg/dl); and agreement to participate in the study.

The exclusion criteria were: type 1 diabetes; any treatment with insulin, sulfonylureas or glinides or other oral or injectable hypoglycemic agents; any previous acute cardiovascular events; no cholesterol-lowering drug treatment; known hypersensitivity / intolerance to BBR or silymarin; and known, severe kidney and/or liver diseases or malignancies

All enrolled subjects were randomized into two groups (68 in each group) to receive either treatment or placebo. Treated subjects took a tablet containing 500 mg BBR and 105 mg silymarin (BS) twice a day (after lunch and dinner). Subjects under placebo (P) took tablets which were indistinguishable from BS in terms of size, shape, color, smell, and taste. Both were administered over a period of 52 weeks.

In greater detail, both medication and placebo packaging intended for couples of paired subjects were prepared by the hospital pharmacy and to each box of pills a serial number was attributed as supplied by a generator of pairs of random numbers corresponding to a package of drug and placebo. This way each component of each pair of matched subjects was administered either drug or placebo.

During the study all patients received a low-calorie diet (20–25% less than the amount of calories required to maintain current weight) characterized by low glycemic index foods and based on a variable percentage of proteins (10–20%), fat (20–30% with less than 10% as saturated fat), and carbohydrates (50–60% with less than 5% as sucrose). Individual dietary regimes were prepared to try and satisfy participant tastes and wishes as much as possible. Favorite carbohydrate sources were starches with a low glycemic index and a high soluble fiber content (35 g/day). At least 30 min per day of predominantly aerobic physical exercise were prescribed.

The following parameters were evaluated at baseline and after 6 and 12 months: fasting blood glucose, fasting serum insulin, HOMA-R (i.e. Insulin Resistance index according to the HOmeostatic Model Assessment), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, uric acid, anthropometric measures (weight, height, BMI, waist circumference or WC, waist to hip ratio), and bioimpedance results (abdominal fat levels).

Safety parameters

AST, ALT, total bilirubin, serum albumin, γ-glutamyl-transferase, alkaline phosphatase, blood urea nitrogen, serum creatinine, red and white blood cell and platelet count, as well as all the above mentioned blood parameters were measured using a high performance autoanalyzer (Automatic biochemistry analyzer with integrated system Selectra Pro XL, Elitech, USA) and an automated blood cell counter (Countess II Automated Cell Counter, Thermo Fisher, USA) at baseline and after 6 and 12 months. Side effects were also recorded at baseline and after 6 and 12 months, using a semi-quantitative scale.

Tested product

In agreement with Italian law number169/2004, the product was notified as Berberol® to the Ministry of Health in 2010 (registration number: E1040753Y) and registered by Pharmextracta (Pontenure,PC, Italy) as a food supplement with both its active ingredients (*Berberis aristata* and *Silybum marianum* standardized extracts) on the positive list of botanicals admitted as nutraceuticals, and with all of its excipients being food grade.

Bioimpedance analysis (BIA)

Abdominal fat was measured with an innovative bioimpedance device (Bia-TANITA AB140 ViScan, BIO) (12), consisting of a band with four electrodes placed directly on the abdomen, with the subject lying supine. The position of the band was guided by a laser beam from the base unit indicating the navel. For high accuracy and repeatability, waist circumference (WC) was measured by the base unit itself with an infrared system. The following parameters were evaluated: WC, trunk fat (TF), and percent visceral fat (VF) at enrollment and after 6 and 12 months of treatment.

Diet adherence

All subjects completed a questionnaire previously validated using a sample of 10 healthcare workers over a 2-week period. It was aimed at evaluating diet adherence during the treatment period. The questionnaire consisted of five questions including the nutritional advice violation rate set and the type and amount of food eaten in excess of the recommended range.

Statistics

The estimated sample size for this study to have a power of 90% with an alpha error of 0.02 to yield a statistically significant result was 50 pairs of subjects. This number was calculated on the basis of the primary outcome endpoint. After taking into consideration the presence of a secondary outcome and the possibility of dropouts, we decided to increase our sample size, including all 68 consecutive pairs of subjects who met the inclusion criteria. Results were expressed as mean ± SD or %. Observed treatment and differences were tested by the repeated measures analysis of variance (rANOVA) integrated by two-tailed paired Student's *t*-test with 95% Confidence Intervals (CI) for parametric variables and Mann–Whitney's U test for non-parametric ones. The χ^2 test with Yates correction or Fisher Exact test was used to compare categorical variables. A $p<0.05$ was chosen as the least acceptable level of statistical significance. All the evaluations were performed using the SPSS/PC+ software (Norusis Inc, Ill, USA).

RESULTS

A total of 136 consecutive subjects meeting the above-mentioned criteria were enrolled during a three-month period and were randomly assigned

to BBR-Sylimarine treatment (68 subjects; BBR Group) or placebo (68 subjects; P Group). No significant differences were found between the two treatment groups at baseline, as described in Table I.

All enrolled patients completed the study. A good adherence to the diet was observed in both groups (89% *vs* 92% in BBR and P, respectively; p n.s.).

The side effects observed were low and quite similar in both groups. In greater detail, the following were recorded in the BBR *vs* the P group, respectively: drowsiness (n=1 *vs* n=1), acid regurgitation (n=2 *vs* n=2), post-prandial nausea/vomiting (n=1 *vs* n=1), itching (n=1 *vs* n=1), headache (n=1 *vs* n=3), dizziness and/or fainting (n=1 *vs* n=1), cold sweat with/without hunger pangs (n=2 *vs* n=3), palpitation (n=2 *vs* n=3), tachycardia (n=1 *vs* n=1). None experienced constipation.

The biochemical safety parameters changed similarly in both groups at the end of treatment with percentage variations between 0.2 and 0.5%.

The studied parameter changes are summarized in Table II, showing a full, significant improvement in the BBR in respect to both baseline and the Placebo Group, peaking at 52 weeks. In greater detail, in fact, HbA1c became significantly lower in the BBR Group but showed only a non-significant decreasing trend in the P Group; a significant beneficial effect was also observed for BBR on uric acid, as well as, on systolic and diastolic blood pressure. The BBR Group also showed a significantly greater percent and absolute decrease in waist circumference than the P Group (16.7% *vs* 13.8% and 15 cm *vs* 6 cm, respectively; p <0.01),

Table I. *Clinically relevant parameters at baseline. As shown, there were no significant differences between the two groups. Absolute, percent or M±SD values are reported.*

	BBR Group	Placebo Group	*p*
Subjects (n.)	68	68	-
Male (n.)	28	28	n.s.
Age (year)	56±8	55±9	n.s.
Waist circumference (cm)	118±9	115±13	n.s.
BMI (kg/m^2)	34±4	34±5	n.s.
Trunk fat level (%)	48±7	45±6	n.s.
Visceral fat level (%)	24±8	22±8	n.s.
Systolic BP (mmHg)	138.3±14.5	137.9±15	n.s.
Diastolic BP (mmHg)	82.9±9.2	81.8±8.9	n.s.
Heart rate (beats/min)	73.0±9.6	72.5±9.7	n.s.
Fasting plasma glucose (mg/dl)	131±22	139±18	n.s.
HOMA-R	3.3±0.2	3.2±0.2	n.s.
eGFR (ml/min/1,73 m^2)	87±9	90±12	n.s.
Total cholesterol (mg/dl)	230±18	237±15	n.s.
HDL cholesterol (mg/dl)	37±7	39±5	n.s.
LDL cholesterol (mg/dl)	107±16	109±14	n.s.
Triglycerides (mg/dl)	198±18	201±15	n.s.
AST (UI/L)	27±9	25±8	n.s.
ALT (UI/L)	29±8	27±9	n.s.
γGT (UI/L)	19±7	21±5	n.s.
Uric Acid (mg/dl)	7.5±1.3	7.4±1.5	n.s.
Cardiovascular risk factors			
Elevated waist-hip ratio (n.)	68	68	n.s.
Recent or current smokers (n.)	16	15	n.s.
Low concentration of HDL cholesterol (n.)	68	68	n.s.
Diabetes mellitus (no.)	68	68	n.s.
Family history of premature heart disease (n.)	14	12	n.s.
Early renal dysfunction (n.)	0	0	-
Hypertension (n.)	59	61	n.s.
≥2 Risk factors (n.)	68	68	n.s.

with abdominal fat redistribution. In fact, the BBR group displayed a 26.2% TF decrease *vs* 2.1% ($p < 0.01$) and a 26.1% VF decrease *vs* 13.6% in the P group ($p < 0.01$) (Fig. 1). As a consequence of this, after treatment also BMI became significantly lower in the BBR group, as shown in Fig. 2.

After 52 weeks, modifiable cardiovascular risk factors displayed the following % improvement with respect to baseline in the BBR *vs* the P group: waist to hip ratio -12.7% *vs* -5.2% ($p<0.001$); HDL cholesterol (mg/dl) +17.2% *vs* +2.4% ($p<0.001$); systolic BP -8.2% *vs* -2.1% ($p<0.01$); diastolic BP -5.9% *vs* -1.5% ($p<0,01$); fasting plasma glucose -25.2% *vs* -10.1% ($p<0.001$) and HbA1c -18.0% *vs* -5.3% ($p<0.001$), respectively.

The 10-year chance of cardiovascular events occurring was calculated on the basis of the CV risk score developed by the Italian Health Institute (ISS, Istituto Superiore di Sanità; "Progetto Cuore") taking into account age, gender, smoking habits, diagnosed diabetes or hypertension, attained blood pressure level, total and HDL cholesterol

Table II. *Effects of a 52-week treatment on biochemical, clinical and bioimpedance parameters (M±SD).*

Comparison of lipidic parameters between treatment groups								
	Total Cholesterol (mg/dl)		HDL Cholesterol (mg/dl)		Triglycerides (mg/dl)		LDL Cholesterol (mg/dl)	
	BBR Group	P Group	BBR Group	P Group	BBR Group	P Group	BBR Group	P Group
Baseline	238±13	233±14	41±3	41±4	198±23	199±18	151±18	153±14
24 weeks	201±14**	217±18	43±4	42±4	176±16*	187±16	123±12*	138±15*
52 weeks	178±16**#	198±17*	48±3*#	42±4	148±13**#	185±15*	100±14**#	119±12*
Comparison of HOMA-R and bioimpedance parameters between treatment groups								
	HOMA-R		WC (cm)		TF (%)		VF (%)	
	BBR Group	P Group	BBR Group	P Group	BBR Group	P Group	BBR Group	P Group
Baseline	4.7±0.4	4.6±0.4	118±7	116±11	48±50	47±5	23±6	23±8
24 weeks	3.4±0.6*	4.4±0.6	106±8*	111±11	41±4*	46±6	19±6*	20±8
52 weeks	2.8±0.5**#	4.3±0.6*	103±5**#	110±04*	40±3**#	46±5	14±4** #	19±9*
Comparison of Uric Acid, HbA1c and blood pressure between treatment groups								
	Uric Acid (mg/dl)		HbA1c (%)		SBP (mmHg)		DBP (mmHg)	
	BBR Group	P Group	BBR Group	P Group	BBR Group	P Group	BBR Group	P Group
Baseline	7.5±1.3	7.4±1.5	7.9±0.5	7.8±0.5	148±12	146±11	98±5	97±5
24 weeks	5.4±0.6**#	7.2±0.9	6.9±0.6*	7.6±0.6	126±18*§	141±11	81±4*	96±6
52 weeks	4.2±0.5**#	7.0±0.5*	6.4±0.6**#	7.4±0.6	123±15**#	138±14**#	78±8**#	95±9

p<0.01, *p<0.05 vs baseline; # p<0.01, § p<0.05 vs Placebo group

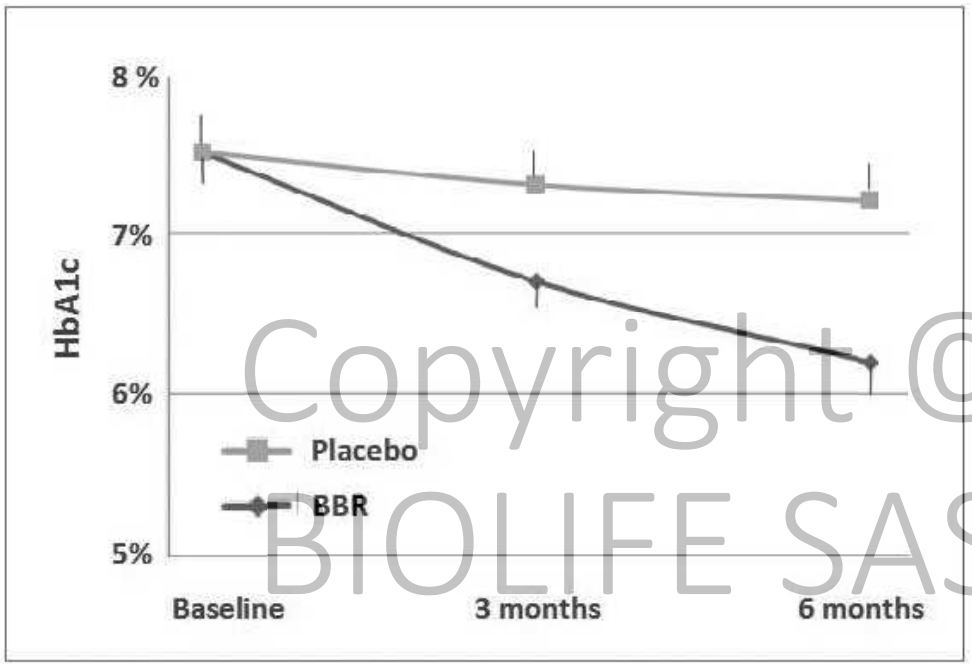

Fig. 1. *Comparison between BBR and Placebo Groups during a 52-week treatment period in respect to HbA1c (M±SD; %) (**<0.01, * p<0.05 vs baseline). Time expressed as months.*

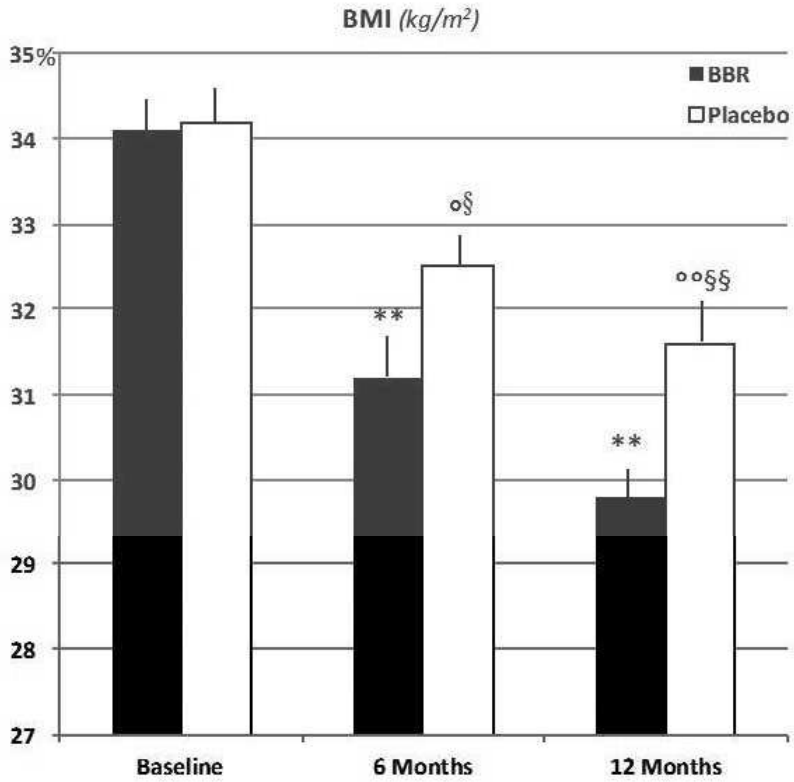

Fig. 2. *Comparison between BBR and Placebo Groups in respect to BMI (M±SD; kg/m²) during a 52-week treatment period (**<0.01 vs baseline; °° p<0.01; °p<0.05 vs baseline; §§ p<0.01 and § p<0.05 vs BBR Group). Time expressed as months.*

(13). The two patient groups displayed statistically undistinguishable risk scores at baseline and were therefore combined and ranked by gender and smoking habits for further analysis: they were 13.3±2.5 (range 9.2-17.7), with a marked difference between nonsmokers and smokers both in males (10.9±1.5, range 8.8-12.1 and 17.5±2.7, range 12.7-20.3, respectively) and in females (10.2±1.3, range 6.7-11.6 and 14.9±2.9, range 11.2-19.1, respectively). After the 52-week treatment period the risk score significantly decreased by a 25-32% range for men and a 8-11% range for women.

DISCUSSION

The BBR–silymarin association is a nutraceutical combination of highly standardized *Berberis aristata* and *Silybum marianum* herbal extracts, titrated as 85% BBR and 60–80% flavolignanes, respectively. In uncontrolled clinical trials BBR seems to have beneficial effects in patients with T2DM with suboptimal glycemic control when given alone (6, 8) or in addition to a conventional treatment regimen (i.e., metformin, dipeptidylpeptidase-4 inhibitors, glitazones, acarbose, or insulin alone or combined with one another), to improve the cholesterol-lowering properties of statins, and to have a positive effect on liver enzymes. Doses utilized in these preliminary studies caused virtually no relevant side effects, as witnessed by the fact that no patients discontinued treatment. The results of a recent pilot study we published on 50 obese hypercholesterolemic people with T2DM treated with BBR for 24 weeks also confirmed the ability of BBR to (i) significantly improve a series of metabolic parameters and body fat distribution, and (ii) affect energy balance at multiple sites by increasing insulin sensitivity, as witnessed by HOMA-R decrease (14).

These results were further supported by the present 52-week placebo-controlled study, showing a significant improvement of all investigated anthropometric, clinical and laboratory parameters in the BBR group.

Another interesting aspect of our study was the decrease of cardiovascular risk score in patients with a high pathological burden, represented by the metabolic syndrome (MS) as defined by the ATP III criteria (15). In fact, due to its mechanism of action, BBR has been extensively used to date in people with high cardiovascular risk factors, such as T2DM, obesity, polycystic ovary syndrome, hyperlipidemia, hypertension, and gut dysbiosis, or with multiple chronic diseases including breast cancer.

The results obtained by others in patients with both subtle and overt glucose metabolism abnormalities and/or hyperinsulinemia and/or metabolic syndrome support the efficacy and safety of BBR in reducing cardiovascular risk factors, and our data provide statistical support to their field observations.

In fact, BBR fulfills various metabolic effects in subjects with MS by: i) exerting a protective role through its cholesterol-lowering activity; ii) protecting against atherosclerosis through its anti-inflammatory, anti-oxidant and smooth muscle cell anti-proliferative properties; iii) improving endothelial dysfunction; iv) lowering uric acid; v) increasing adipose and muscle cell glucose utilization, as well as, vi) decreasing gut glucose absorption and, consequently, body weight. The treatment seems to be safe and tolerated at the tested doses, with minimal unwanted effects, which in most cases tend to resolve spontaneously during treatment.

The originality of our findings lies in the following facts: (i) the study was conducted for 52 weeks on a homogeneous series of subjects with metabolic syndrome; (ii) a significantly lower abdominal adiposity was attained with BBR; and (iii) for the first time a significant decreasing effect was described with BBR on circulating uric acid.

Our results need further confirmation in larger trials, of course, but point to a new possible clinical use of BBR aimed at treating abdominal fat in overweight/obese patients with T2DM.

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