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ORIGINAL RESEARCH

An Evaluation of a Nutraceutical with Berberine, Curcumin, Inositol, Banaba and Chromium Picolinate in Patients with Fasting Dysglycemia

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Giuseppe Derosa[1–3]
Angela D'Angelo[1,2]
Arianna Vanelli[4]
Pamela Maffioli[1,3]

[1]Center of Diabetes and Metabolic Diseases, Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Laboratory of Molecular Medicine, University of Pavia, Pavia, Italy; [3]Center for Prevention, Surveillance, Diagnosis and Treatment of Rare Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [4]Nutrilinea srl, Gallarate, Italy

Aim: To evaluate if a nutraceutical containing Berberine, Curcumin, Inositol, Banaba, and Chromium Picolinate (Reglicem®), can ameliorate glycemic status in patients with dysglycemia.
Methods: We enrolled 148 patients with impaired fasting plasma glucose or impaired glucose tolerance, not taking any hypoglycemic compounds. Patients were randomized to take nutraceutical or placebo for 3 months, in a randomized, double-blind, placebo-controlled design. Both nutraceutical and placebo were self-administered once a day, 1 tablet during the breakfast.
Results: A reduction of fasting and post-prandial plasma glucose was observed with the nutraceutical combination ($p < 0.05$ vs baseline and $p < 0.05$ vs placebo, respectively). Furthermore, a decrease of glycated hemoglobin, and fasting plasma insulin was observed with the nutraceutical combination ($p < 0.05$ vs baseline and $p < 0.05$ vs placebo, respectively). Then, there was a reduction of homeostasis model assessment index with the nutraceutical combination ($p < 0.05$ vs baseline and $p < 0.05$ vs placebo). M value was higher ($p < 0.05$ vs baseline and $p < 0.05$ vs placebo) in the nutraceutical combination group at the end of the treatment. We observed a reduction of total cholesterol (TC) ($p < 0.05$ vs baseline) and triglycerides (Tg) ($p < 0.05$ vs baseline and $p < 0.05$ vs placebo) with the nutraceutical combination, respectively. Finally, high sensitivity C-reactive protein was reduced after 3 months with nutraceutical combination therapy ($p < 0.05$ vs baseline and $p < 0.05$ vs placebo, respectively).
Conclusion: A nutraceutical containing Berberine, Curcumin, Inositol, Banaba, and Chromium Picolinate can be helpful in improving glyco-metabolic compensation, TC and Tg value, and in reducing inflammatory status in patients with dysglycemia.
Keywords: Berberine, Curcuma, Inositol, Banaba, Chromium Picolinate, dysglycemia

Introduction

The euglycemic status is a range between 70 and 99 mg/dl. This range is controlled by the counterbalance of two hormones: glucagon, hyperglycemic agent secreted by α-pancreatic cells and insulin, hypoglycemic agent secreted by β-pancreatic cells. Muscle, adipose tissue and liver have the possibility of glucose uptake. The variation of glycemic balance can lead to cardiovascular disorders. Dysglycemia is an important pre-risk condition. To treat the pre-risk factor effectively (and therefore, prevent it), we need to treat patients with behavioural therapies (an appropriate diet with respect to quality and quantity and regular physical activity, that is, 30–40 mins, at least 3 or 4 times a week) and with the appropriate nutraceutical. Treating patients with a nutraceutical means

Correspondence: Giuseppe Derosa
Department of Internal Medicine and Therapeutics, University of Pavia, and Fondazione IRCCS Policlinico San Matteo, P.le C. Golgi, 2, Pavia 27100, Italy
Tel +39-0382 526217
Fax +39-0382 526259
Email giuseppe.derosa@unipv.it

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preventing the mechanism underlying the pathology from making its "normal" course which would otherwise result in the "overt pathology".[1]

Various studies demonstrated that the use of Berberine,[2–5] or Banaba,[6] or Chromium Picolinate[7,8] improved dysglycemia, insulin-resistance status, some anthropometric parameters, and lipid metabolism related to metabolic syndrome.

Berberine would improve dysglycemia by activating adenosine monophosphate-activated protein kinase (AMPK) and increasing phosphorylation of the insulin receptor;[9] the positive effects of Berberine on glycemia and insulin resistance have already been demonstrated by our group in a previous study.[4]

The hypoglycemic effects of Banaba are attributable to corosolic acid and ellagitannins. Previous studies have demonstrated ellagitannins stimulates glucose uptake in adipocytes of rats,[10] while corosolic acid stimulates glucose uptake by tumor cells.[11] These mechanisms could be managed by the hypoglycemic agent of Banaba extracts.

As for Chromium, it is a necessary cofactor for many actions of insulin, because it promotes its binding to its receptors in striated muscle cells, in adipocytes and in hepatocytes and promotes phosphorylation of receptors. These mechanisms contribute to glucose transport in the liver, muscle, and adipose tissue, improving glucose tolerance.[12] Human studies have shown that Curcumin consumption improves insulin sensitivity[13] and has positive effects on metabolic disorders related to it such as metabolic syndrome[14,15] and impaired glucose tolerance (IGT).[16] It has been observed that Curcumin, in a highly water dispersible formulation, improves glucose tolerance by stimulating the secretion of incretin glucagon-like peptide 1 (GLP-1).[17]

Regarding inositol, it has been shown that some isomers, myo-inositol and D-chiro-inositol, perform the function of second messengers of insulin:[18] clinical studies have shown that taking these compounds improves insulin resistance and reduces cardiovascular risk factors in women with polycystic ovary syndrome,[19,20] gestational diabetes mellitus[21,22] and metabolic syndrome post-menopause.[23,24]

The aim of this study was to evaluate the effects of a nutraceutical containing Berberine, Curcumin, Inositol, Banaba, and Chromium Picolinate (Reglicem®) on the regression of the impaired fasting glucose (IFG) or IGT condition in patients with dysglycemia and on the glycolipid metabolism in patients with IFG or IGT status.

Materials and Methods

Study Design

This 3-months, double-blind, randomized, placebo-controlled, clinical trial was conducted at the Centre of Diabetes and Metabolic Diseases, Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico San Matteo, PAVIA, Italy.

The study protocol was approved by the review board of Fondazione IRCCS Policlinico San Matteo, PAVIA, Italy and was conducted in accordance with the 1994 Declaration of Helsinki,[25] and its amendments and the Code of Good Clinical Practice. TRIAL REGISTRATION: ClinicalTrials.gov NCT04107987. All patients provided written informed consent to participate in this study after a full explanation of the study.

Patients

We enrolled patients with IFG or IGT, not taking any hypoglycemic drugs (both pharmaceuticals or nutraceuticals). Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had type 1 or type 2 diabetes mellitus, impaired hepatic function (defined as transaminases and/or gamma-glutamyl transpeptidase (γ-GT) level higher than the three times the upper limit of normal [ULN] which was 39 mU/mL for aspartate transaminase (AST), 34 mU/mL, for alanine transaminase (ALT) and 53 mU/mL for γ-GT, impaired renal function (defined as serum creatinine level higher than the ULN which was 1.18 mg/dl), or gastrointestinal disorders. We also excluded patients with current or previous evidence of ischemic heart disease, heart failure, or stroke; malignancy, and significant neurological or psychiatric disturbances, including alcohol or drug abuse. Excluded medications (within the previous 3 months) included hypoglycemic agents, laxatives, β-agonists (other than inhalers), cyproheptadine, anti-depressants, anti-serotoninergics, phenothiazines, barbiturates, oral corticosteroids, and anti-psychotics. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

Treatments

Patients were randomized to take a nutraceutical containing Berberine, Curcumin, Inositol, Banaba, and Chromium Picolinate (Reglicem) (Table 1) or placebo once a day, 1 tablet during the breakfast for 3 months, in a randomized,

Table 1 Composition of the Nutraceutical and Placebo

Ingredients	Daily Intake
Nutraceutical	
Chromium Picolinate (with 12.5% Chromium)	100 μcg Cr (250% RDD)
Curcumin dry extract with 95% curcumins	200 mg
Berberine dry extract with 98% berberine	200 mg
Inositol	300 mg
Banaba dry extract with 1% corosolic acid	40 mg
Silicon Dioxide	q.s
Magnesium Stearate	q.s
Dicalcium Phosphate	q.s
Microcrystalline Cellulose	q.s
Placebo	
Silicon Dioxide	q.s
Magnesium Stearate	q.s
Dicalcium Phosphate	q.s
Microcrystalline Cellulose	q.s

Abbreviations: RDD, Recommended Daily Dose; q.s, quantum sufficit.

double-blind, placebo-controlled design. Both nutraceutical and placebo were produced and provided for free by Nutrilinea s.r.l. (Gallarate, Varese, ITALY).

Both nutraceutical and placebo were supplied as identical, opaque, tablets in coded bottles to ensure the blind status of the study. Randomisation was done using a drawing of envelopes containing randomisation codes prepared by a statistician. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a 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), assessment of fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), glycated haemoglobin (HbA_{1c}), fasting plasma insulin (FPI), homeostasis model assessment index (HOMA index), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), AST, ALT, high-sensitivity C-reactive protein (Hs-CRP).

All parameters were assessed at baseline and after 3 months since the study start. Moreover, at baseline, and after 3 months, patients underwent an oral glucose tolerance test (OGTT), and an euglycemic hyperinsulinemic clamp. For a description of how various parameters were evaluated, please see our previous paper.[26]

Transaminases were evaluated in central laboratory according to standard methods.

Safety Measurements

Treatment tolerability was assessed using an accurate interview of patients by the clinicians at each study visit, and comparisons of clinical and laboratory values with baseline levels. Safety monitoring included physical examination, vital sign assessment, weight, electrocardiogram, adverse events, and laboratory tests. Liver function was evaluated by measurement of transaminases (AST, ALT), and all adverse events were recorded.

Oral Glucose Tolerance Test

All subjects drank a glass of water (200 mL), in which 75 g of glucose had been dissolved over a period of 5 min in the morning, between 8 and 9 a.m. after a 12-h fast, and after dietary assessment to ensure a carbohydrate intake > 150 g/day over the previous 3 days.[27] Normal physical activity was allowed over the previous 3 days. No smoking was allowed during the test. Blood samples were collected in EDTA-containing tubes (Becton Dickinson, Meylan Cedex, France) through a venous catheter from an antecubital vein immediately before and at 120 min after the glucose load for the measurement of the considered parameters of the study. On the basis of the results recorded 2 hrs after the OGTT, we diagnosed patients as being affected by IFG, IGT or type 2 diabetes mellitus. In particular:

- IFG: was defined by glycemia at 120 mins from OGTT < 140 mg/dl;
- IGT: was defined by glycemia at 120 mins from OGTT between 140 mg/dl and 199 mg/dl;
- type 2 diabetes mellitus: was defined by glycemia at 120 mins from OGTT ≥ 200 mg/dl.

Glucose Clamp Technique

An euglycemic hyperinsulinemic clamp was performed to assess insulin sensitivity.[28]

Clamps were performed before randomization, and at the end of the study. At 9:00 AM, after the patients had fasted for

12 hrs overnight, an indwelling cannula (18-gauge polyethylene cannula; Venflon, Viggo, Helsingborg, SWEDEN) was placed into an antecubital vein for infusion of glucose and insulin. To obtain arterialized venous blood samples, an indwelling was inserted in a retrograde fashion into a dorsal hand or wrist vein and maintained in a heated box at 70°C. In the contra lateral arm, a second cannula was introduced anterogradely in an antecubital vein of the forearm for the variable infusion of 20% glucose (L.I.M., Biondustria, Novi Ligure, AL, ITALY) and insulin (1 mU min^{-1} Kg^{-1}, Humulin R, Eli Lilly, Indianapolis, IN, USA, using a Terumo microinfusion pump, TE-371 TIVA, Terumo Corporation, Tokyo, JAPAN). Arterialized blood samples were collected every 5 min to determine glucose concentration (EML 105, Radiometer, Copenhagen, DENMARK). The amount of glucose infused was adjusted to maintain euglycemia at 90 mg/dl. During the euglycemic hyperinsulinemic clamp, the M-value was calculated based on the last 30 min (steady state) and after adjustments for steady-state insulin concentration (M/I).

Statistical Analysis

An intention-to-treat (ITT) analysis was conducted in patients who had received ≥1 dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received ≥1 dose of trial medication after randomization and had undergone a subsequent tolerability observation. Continuous variables were tested using a two-way repeated measures analysis of variance (ANOVA). Intervention effects were adjusted for additional potential confounders using analysis of covariance. Analysis of variance was also used to assess the significance within and between groups.

The null hypothesis that the expected mean glycemia change from the end of the study did not differ significantly between placebo, and nutraceutical was tested using a two-way repeated measures analysis of variance (ANOVA) model.[29] Similar analyses were applied to the other variables. A 1-sample *t*-test was used to compare values obtained before and after treatment administration; 2-sample *t*-tests were used for between-group comparisons. Integration (area under the curve) was carried out using the trapezoidal rule. Integrated incremental responses describe changes above baseline. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 14.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean (SD). For all statistical analyses, $p< 0.05$ was considered statistically significant.

Results

Study Sample

A total of 148 patients were enrolled in the trial. Of these, 73 were randomized to nutraceutical, and 75 to placebo. One hundred and forty patients completed the study; there were 8 patients who did not complete the study and the reasons for premature withdrawal included non-compliance to treatment or lost to follow-up. The characteristics of the patient population at the study entry, and during the study, are shown in Tables 2–3.

Anthropometric Parameters and Glycemic Metabolism

No variations of BMI or circumferences were recorded with neither treatments (Table 3).

A reduction of FPG and PPG was recorded with the nutraceutical combination compared to baseline ($p < 0.05$, respectively), and compared to placebo ($p < 0.05$, respectively). A change of HbA_{1c}, FPI, were recorded with the nutraceutical combination ($p < 0.05$ vs baseline, and vs placebo, respectively). Regarding insulin resistance, there was a decrease of HOMA index with the nutraceutical combination compared to baseline ($p < 0.05$), and to placebo ($p < 0.05$), respectively (Table 3).

Table 2 Baseline, and 3 Months Data of Patients During Nutraceutical Treatment and Placebo

Parameters	Nutraceutical		Placebo	
	Baseline	3 Months	Baseline	3 Months
Patients (n)	73	70	75	70
M/F	35/38	32/38	38/37	36/34
Smoking status (M/F)	14/16	12/16	15/13	14/11
IFG (n; %)	20/22 (57.5)	10/12 (31.4)	23/22 (60.0)	18/14 (45.7)
IGT (n; %)	15/16 (42.5)	12/12 (34.3)	15/15 (40.0)	15/17 (45.7)
EU from IFG (n; %)	–	9/8 (24.3)	–	0/0
EU from IGT (n; %)	–	3/4 (10.0)	–	0/0
IGT from IFG (n: %)	–	0/0	–	3/5 (11.4)
D from IFG (n; %)	–	0/0	–	0/0
D from IGT (n; %)		0/0	–	3/3 (8.6)
Lost to FU from IFG (n; %)	–	1/2 (4.3)	–	2/3 (7.1)
Lost to FU from IGT (n; %)	–	0/0	–	0/0

Abbreviations: M, males; F, females; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; EU, euglycemia; D, diabetes; FU, follow-up.

Table 3 Baseline, and 3 Months Data of Patients During Nutraceutical Treatment and Placebo

Parameters	Nutraceutical			Placebo			p-value Nutraceutical vs Placebo
	Baseline	3 Months	p-value vs Baseline	Baseline	3 Months	p-value vs Baseline	
Patients	73	70		75	70		
M/F	35/38	32/38		38/37	36/34		
Age (years)	55.8 ± 8.3	-		56.9 ± 8.7	–		
Smoking status (M/F)	14/16	12/16		15/13	14/11		
Height (cm)	1.68 ± 0.04	1.68 ± 0.04	0.142	1.69 ± 0.05	1.69 ± 0.05	0.145	0.139
Weight (Kg)	80.1 ± 9.7	79.5 ± 9.4	0.231	81.5 ± 9.9	81.9 ± 10.3	0.238	0.244
BMI (Kg/m^2)	28.4 ± 2.3	28.2 ± 2.1	0.346	28.5 ± 2.4	28.7 ± 2.5	0.355	0.316
WC (cm)	89.4 ± 3.1	88.2 ± 2.8	0.397	89.9 ± 3.4	90.6 ± 3.8	0.403	0.453
HC (cm)	86.3 ± 2.4	86.1 ± 2.2	0.374	86.7 ± 2.6	87.8 ± 3.1	0.382	0.393
AC (cm)	97.1 ± 3.0	96.3 ± 2.7	0.426	98.1 ± 3.3	98.9 ± 3.7	0.431	0.433
FPG (mg/dl)	117.4 ± 7.7	102.4 ± 7.0*^	0.041	114.3 ± 7.1	116.5 ± 11.4	0.376	0.048
PPG (mg/dl)	128.2 ± 13.6	118.5 ± 7.2*^	0.037	129.1 ± 7.3	130.6 ± 7.7	0.326	0.042
HbA_{1c} (%)	6.0 ± 0.4	5.6 ± 0.2*^	0.035	5.9 ± 0.3	5.8 ± 0.3	0.416	0.045
FPI (μU/mL)	8.9 ± 5.1	9.5± 5.3*^	0.032	9.0 ± 5.2	8.9 ± 5.1	0.459	0.037
Homa index	2.57 ± 0.8	2.39 ± 0.7*^	0.037	2.56 ± 0.7	2.51 ± 0.5	0.363	0.032
TC (mg/dl)	215.1 ± 18.3	202.6 ± 17.2*	0.042	213.6 ± 17.9	209.4 ± 16.9	0.248	0.074
LDL-C (mg/dl)	144.3 ± 17.4	134.3 ± 14.2	0.076	143.1 ± 16.8	138.7 ± 15.8	0.252	0.091
HDL-C (mg/dl)	45.1 ± 4.8	46.3 ± 5.1	0.178	45.5 ± 4.9	44.2 ± 4.5	0.293	0.141
Tg (mg/dl)	128.3 ± 36.3	110.2 ± 31.4*^	0.034	125.2 ± 35.9	132.4 ± 37.1	0.167	0.039
AST (UI/l)	18.4 ± 8.3	17.8 ± 8.1	0.189	18.5 ± 8.6	18.1 ± 9.2	0.293	0.161
ALT (UI/l)	23.2 ± 13.6	21.9 ± 12.1	0.157	22.1 ± 12.5	23.6 ± 13.9	0.187	0.173
Hs-CRP (mg/l)	1.2 ± 0.7	0.9 ± 0.6	0.069	1.0 ± 0.5	1.2 ± 0.7	0.163	0.082

Notes: Data are expressed as mean ± standard deviation. *$p < 0.05$ vs baseline; ^$p < 0.05$ vs placebo.
Abbreviations: M, males; F, females; BMI, body mass index; WC, waist circumference; HC, hip circumference; AC, abdominal circumference; FPG, fasting plasma glucose; PPG, postprandial glucose; HbA_{1c}, glycated hemoglobin; FPI, fasting plasma insulin; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; Tg, triglycerides; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hs-CRP, high-sensitivity C-reactive protein.

OGTT Results

At baseline, 57.5% of patients were affected by IFG in the nutraceutical group vs 60.0% in placebo (p not significant), while 42.5% of patients were affected by IGT in the nutraceutical group, and 40.0% in placebo group (p not significant). After 3 months, 34.3 % of patients returned to a normal glycemic status in the nutraceutical group vs 0 patients in placebo group; at the end of the study, 31.4% were classified as IFG in the nutraceutical group vs 45.7% in placebo group. In the nutraceutical group, 34.3% were classified as IGT vs 45.7% in placebo group. In placebo group, 11.4% were classified as IGT from IFG group, while no patients have worsened its category in nutraceutical group. In placebo group, 8.6% developed type 2 diabetes mellitus vs 0 patients in the nutraceutical group (Tables 2 and 4(A and B)).

M Value During Clamp Technique

M value obtained after nutraceutical treatment was higher compared to baseline ($p < 0.05$). No significant variation was recorded with placebo compared to baseline. Moreover, M value recorded with nutraceutical was higher than the one observed with placebo ($p < 0.05$).

Considering as normal insulin sensitivity a M value ≥ 7.5 mg/kg/min, at the end of the study, more patients returned to insulin sensitivity (69%) with the nutraceutical treatment compared to placebo. Moreover, 31% of patients reached an M value ≥ 4 and < 7.5 mg/kg/min, and 0 patients had insulin resistance at the end of the study in the nutraceutical treatment (Table 5).

Lipid Profile

No variation was obtained on LDL-C and HDL-C with neither treatments.

We observed a decrease of TC with the nutraceutical combination with respect to baseline ($p < 0.05$) and a reduction of Tg with the nutraceutical combination compared to baseline ($p < 0.05$) and compared to placebo ($p < 0.05$), respectively (Table 3).

Table 4 (**A**) Results of the Randomized Patients, After OGTT at Baseline. (**B**) Results of the Randomized Patients, After OGTT at the End of the Study

	Time (Minutes)	Nutraceutical		Placebo	
		Glycemia (mg/dl)	Subjects (n, M/F)	Glycemia (mg/dl)	Subjects (n, M/F)
A. Baseline					
IFG	0 120	114.3 ± 9.6 124.2 ± 13.7	42 (20/22)	113.2 ± 8.9 122.9 ± 12.3	45 (23/22)
IGT	0 120	115.1 ± 10.2 165.8 ± 19.1	31 (15/16)	114.8 ± 10.0 161.3 ± 18.2	30 (15/15)
B. End of the Study					
IFG	0 120	103.7 ± 2.9 111.8 ± 9.1	22 (10/12)	106.8 ± 6.1 122.4 ± 13.9	32 (18/14)
IGT	0 120	104.9 ± 4.6 147.2 ± 5.8	24 (12/12)	107.9 ± 7.2 151.2 ± 10.5	32 (15/17)

Note: Data are means ± SD.
Abbreviations: n, number of subjects; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table 5 Baseline, and 3 Months Data of Clamp (M Value) in Patients Treated with Nutraceutical or Placebo

	N Baseline	N End of Treatment	Baseline	End of Treatment	Delta End of Treatment vs Baseline
Nutraceutical Placebo	73 75	70 70	5.94 ± 0.97 5.89 ± 1.02	7.97 ± 1.32*° 5.96 ± 1.07	2.03 ± 0.86 0.07 ± 0.06

Notes: Data are expressed as SD: standard deviation. *$p < 0.05$ vs baseline; °$p < 0.05$ vs placebo. Definition of insulin sensitivity: Normal insulin sensitivity: M value ≥ 7.5 mg/kg/min. Impaired glucose tolerance: M value ≥ 4 and < 7.5 mg/kg/min. Insulin resistance: M value < 4 mg/kg/min.

Cytokines

A reduction of Hs-CRP was recorded with the nutraceutical combination compared to baseline ($p < 0.05$) and compared to placebo ($p < 0.05$), respectively (Table 3).

Safety and Treatment Acceptance

No significant variations of transaminases were recorded during the study. Considering a score among 1 and 10, where 1 is the worst, and 10 is the best, no differences were recorded between groups regarding the acceptance of treatment that was well tolerated.

Discussion

In this study, we showed that a nutraceutical containing Berberine, Curcumin, Inositol, Banaba, and Chromium Picolinate improved glycemic parameters, parameters related to insulin resistance, lipid profile and also the inflammatory status in patients with IFG or IGT, configuring a framework of pre-diabetes.

The glucose regulation of Berberine may enhance the expression of GLUT-4 receptors and the secretion of GLP-1 incretin, and this action can lead to various mechanisms as an increase of insulin secretion, a stimulation of glycolysis, an increase of glucokinase activity, a suppression of adipogenesis, and an inhibition of mitochondrial function.[30] Regarding the effects on glycemia and insulin secretion, a previous study by Di Pierro et al reported Berberine reduced HbA_{1c} of 0.85% after 3 months of treatment, which was maintained after 6 months of treatment.[31] Our group demonstrated an improvement of glycemic control with Berberine during glucagon test and we reported a lower increase in FPG and a greater increase in C-peptide after 6 min from the administration of glucagon, both at baseline and at the end of the trial.[4]

This study confirms these previous data, with FPG decrease of 15 mg/dl (−12.8%), PPG decrease of 9.7 mg/dl (−7.6%), HbA_{1c} decrease of 0.4% (−6.7%), and Homa index decrease of 0.18 (−7.0%) and improvement of FPI secretion of 0.6 μU/mL (+6.7%). A further confirmation can be deduced by the improvement of OGTT at the end of the study and by the increase of the insulin sensitivity determined through euglycemic hyperinsulinemic clamp.

The hypocholesterolemic action of Berberine has been suggested in humans and appears to be mainly due to cholesterol receptors upregulation, MAPK/ERK pathway modulation and PCSK9 inhibition.[30] Derosa et al had already conducted various trials demonstrating Berberine reduced TC by 11.6% and Tg by 21.2% in a trial vs placebo after 3 months from randomization,[32] and TC by 23.2% and Tg by 32.3% in a study compared to placebo after 3 months from the study beginning.[33] In this trial we observed a TC reduction of 12.5 mg/dl (−5,8%) and a Tg reduction of 18.1 mg/dl (−14.1%), confirming a trend of reduction evaluated in previous studies of our group. A possible explanation of this low reduction might be given by the quantity of Berberine (200 mg) present in the studied nutraceutical, compared to a dose used in previous our studies (1000 mg) or by different oral bioavailability.

The role of polyphenol Curcumin on various biological and pharmacological aspects is documented;[34] anyway, the direct action on glucose metabolism in humans is under investigation. The hypoglycemic activity of Banaba (extract standardized to 1% corosolic acid as our formulation) has been already studied by Judy et al[35] in type 2 diabetic patients for 2 weeks. He obtained a 30% decrease in glycemia. It is not clear whether the observed effect was due to corosolic acid or to other components. We used the same dry extract with 1% corosolic acid (40 mg), but with other components.

The supplement of myo-inositol or D-chiro-inositol is well-investigated in women with various conditions, but the effect of Inositol on glucose homeostasis is not well-characterized. Abnormalities in inositol metabolism have been associated with the development of insulin resistance.[36] The studied nutraceutical has 300 mg of Inositol and we have very few data on dysglycemic patients. Furthermore, Chromium Picolinate is necessary as cofactor for many actions of insulin and we can image a synergistic action with Berberine, Curcumin, Banaba, and Inositol on amelioration of glycemic parameters and on lipid improvement and maybe on inflammatory status.

The force of our study is the assessment of insulin resistance (supported by dysglycemia) with euglycemic hyperinsulinemic clamp. The percentage of patients that came back to have euglycemia (<100 mg/dl) is 34.3%, but all patients reported a decrease in blood glucose. The total number of patients of our study had an improvement of insulin resistance and 63% of patients with M value of normal insulin sensibility and 37% of patients with M value testifying an improvement of dysglycemia and a percentage equal to 0% of patients with a worsening of insulin resistance.

We need to observe these changes in a longer period of observation and to verify the possible reversible effect when interrupted such a nutraceutical therapy. Therefore, other trials are needed also to verify the single action of that particular agent on a specific parameter, and may compare the action of a single compound with the mixture of them to test if the observed effects resulted from the activity of the mixture as a whole rather than from each single compound/extract.

Conclusions

We can summarize a nutraceutical product containing Berberine, Curcuma, Inositol, Banaba, and Chromium Picolinate can be helpful in improving glyco-metabolic compensation, TC and Tg value, and in reducing inflammatory status in patients with dysglycemia.

Data Sharing Statement

To protect patients' privacy, such as written informed consent signed by patients, the authors cannot share data.

Author Contributions

Design and conduction of the study: Giuseppe Derosa and Pamela Maffioli; data collection: all authors; data interpretation and manuscript writing: Giuseppe Derosa and Pamela Maffioli. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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