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Improved metabolic control by *Ipomoea batatas* (Caiapo) is associated with increased adiponectin and decreased fibrinogen levels in type 2 diabetic subjects

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Aim: The extract of the white-skinned sweet potato *Ipomoea batatas* (Caiapo) has been shown to ameliorate glucose control by improving insulin sensitivity in patients with type 2 diabetes mellitus (T2DM). The present study was designed to further evaluate its mode of action on insulin sensitivity over an extended period of time as well as the effects on fibrinogen and other markers of low-grade inflammation.

Methods: In this randomized trial, 27 patients with T2DM on diet only received 4 g of Caiapo daily for 5 months; 34 patients placebo. Before and after therapy, insulin sensitivity [oral glucose insulin sensitivity (OGIS), as glucose clearance from oral glucose tolerance test], parameters of diabetes control, lipids, plasma adiponectin, high-sensitivity C-reactive protein (hs-CRP) and fibrinogen were measured.

Results: Following Caiapo, we observed an increase in OGIS (293 ± 15 vs. 321 ± 12 ml/m^2/min, p = 0.0072) and adiponectin (5.97 ± 0.65 to 6.63 ± 0.70 μg/ml, p = 0.013), while fibrinogen decreased from 3.83 ± 0.16 to 3.64 ± 0.18 mg/ml (p = 0.02). This was associated with an improvement in glycated haemoglobin (HbA1c: 6.46 ± 0.12 vs. 6.25 ± 0.11%, p = 0.008), fasting glucose (138 ± 4 vs. 128 ± 5 mg/dl, p = 0.039) and triglycerides (2.36 ± 0.22 vs. 2.07 ± 0.25 mmol/l, p = 0.032). Body weight, lipid levels and hs-CRP were not altered. No changes were observed in the placebo group except for HbA1c, which significantly increased from 6.25 ± 0.10 to 6.50 ± 0.12% (p = 0.0001).

Conclusions: This study confirms the beneficial effects of Caiapo on glucose and HbA1c control in patients with T2DM after 5 months follow-up. Improvement of insulin sensitivity was accompanied by increased levels of adiponectin and a decrease in fibrinogen. Thus, Caiapo can be considered as natural insulin sensitizer with potential antiatherogenic properties.

Keywords: beta cell function, glycated haemoglobin, high-sensitivity C-reactive protein, insulin sensitivity, lipid profile, oral glucose tolerance test

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Introduction

Type 2 diabetes mellitus (T2DM) usually develops within the context of the metabolic syndrome, which is characterized by visceral fat accumulation and insulin resistance [1]. As a consequence, dyslipidaemia, hypertension and an increase in non-traditional cardiovascular risk factors such as inflammatory [high sensitivity C-reactive protein (hs-CRP)] and coagulation (fibrinogen) factors occur and contribute to the

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increased cardiovascular morbidity and mortality [2]. Improvement of insulin resistance by lifestyle modification and/or pharmaceutical treatment leads to an amelioration of diabetes control as well as associated risk factors, which will consecutively reduce the risk for diabetic complications [3]. In recent times, insulin sensitizers such as rosiglitazone and pioglitazone have been licensed for the treatment of T2DM [4]. Their use, however, might be limited by side effects such as weight gain, oedema and heart failure. In addition to conventional drugs, attention has been recently directed to neutraceutical products for the treatment of diabetes. While some of these compounds show promising results [5], because of the lack of controlled studies on their effectiveness and safety, they cannot be recommended as alternative treatment of diabetes mellitus.

We have previously assessed the tolerability and the efficacy of Caiapo (an extract from the skin of *Ipomoea batatas*, a potato cultivated in the Kagawa region of Japan) in Caucasian patients with T2DM [6–8]. In a pilot study in 12 subjects, we could demonstrate that Caiapo at the dose of 4 g/day for 6 weeks lowered fasting blood glucose by improving insulin sensitivity [6,7]. Caiapo was subsequently administered for 12 weeks to a larger cohort of T2DM patients with a mild degree of fasting hyperglycaemia and stable physical activity and diet. The results showed a significant improvement of diabetes control as indicated by a decrease in glycated haemoglobin, HbA1c [8]. The systematic evaluations of insulin action during oral and intravenous glucose tests revealed that Caiapo acts via increased insulin sensitivity [7,8], suggesting that this compound may have the properties of a natural insulin sensitizer. In both studies, no weight gain or oedema was observed. While the single compound responsible for the mode of action of Caiapo has not yet been completely identified, the similar mode of action with the glitazones raises some questions about a possible mechanism to improve insulin sensitivity such as an increase in adiponectin and about an influence on inflammatory or procoagulant markers following treatment with Caiapo.

This multicentre study was therefore designed to expand the knowledge about the efficacy and mode of action of Caiapo in diet only–treated patients with T2DM over a longer period of time. In addition, we sought to elucidate a possible relationship between the improvement of insulin sensitivity and circulating adiponectin levels and between diabetes control and markers of inflammation and coagulation.

Methods

The recruitment involved 88 patients, but only 61 completed the study. Reasons for dropping out were pregnancy in one subject and non-compliance regarding follow-up visits, partially because of the flooding of the river Elbe. Sample size was evaluated based upon previous studies [6,8] and suggested that 21 subjects per group were required. Sixty one patients with T2DM were analysed in this randomized, double-blind, placebo-controlled trial: 27 received Caiapo (14 males, 13 females, age 57.2 ± 1.8 years, diabetes duration 3.5 ± 0.8 years, blood pressure 137/84 ± 3/2 mmHg) and 34 placebo (18 males, 16 females, age 61.1 ± 1.5, diabetes duration 4.2 ± 0.5, blood pressure 138/84 ± 3/2). Other patients' characteristics at baseline are shown in table 1. One month after screening, patients were enrolled after signing the informed consent, reviewed and approved together with the protocol by independent Ethics Committees in Austria and Germany. The study was performed according to the Declaration of Helsinki, as amended in 2000 in Edinburgh in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (Topic E6, CPMP/ICH 135/95, 07/1996; post step 4 errata, 09/1997).

Following a baseline 75 g oral glucose tolerance test (OGTT) with measurement of glucose, insulin and free fatty acid (FFA) concentrations before glucose administration and at 30, 60, 90, 120 and 180 min, the subjects were randomized to either treatment with two daily tablets of Caiapo (a total of 4 g) or placebo before breakfast for 5 months. Fasting glucose and insulin were regularly measured in the clinic and the OGTT was repeated at the end of the study period (final visit). No medication considered to affect the validity of the study such as corticosteroids, high-dose diuretics or betablockers was allowed within 2 weeks before screening and during the entire study. No hypoglycaemic drugs were taken since 4 weeks before baseline visit. All patients were advised to keep a weight maintaining diet (28–32 kcal/kg body weight) consisting of 55% carbohydrate, 30% fat and 15% protein. Patients were allowed to consume alcohol if they were in the habit of doing so, but no more than 60 g/day of alcohol for males and 40 g/day for females. The physical activity of the patients was maintained at a constant level throughout the entire period of the study.

Plasma glucose was measured by the hexokinase method using an Express Plus analyzer [BayerVital Diagnostics, Fernwald, Germany; interassay coefficient of variation (ICV) 2.1%]. Specific insulin (failing cross-reactivity with human proinsulin) was determined by

Table 1 Fasting metabolic and lipid parameters before assumption of Caiapo or placebo (baseline) and after 5 months of Caiapo or placebo administration (final visit)

Parameter	Baseline	Final visit	P value
Caiapo			
BMI (kg/m^2)	31.1 ± 0.7	30.7 ± 0.7	0.15
HbA1c (%)	6.46 ± 0.12	6.25 ± 0.11	0.008
Fasting glucose (mg/dl)	138 ± 4	128 ± 5	0.039
Fasting insulin (μU/ml)	20.7 ± 2.2	17.6 ± 1.7	0.06
Total cholesterol (mmol/l)	5.52 ± 0.22	5.34 ± 0.21	0.17
HDL cholesterol (mmol/l)	1.17 ± 0.06	1.21 ± 0.06	0.15
LDL cholesterol (mmol/l)	3.29 ± 0.20	3.23 ± 0.19	0.367
Triglycerides (mmol/l)	2.36 ± 0.22	2.07 ± 0.25	0.032
FFA (mmol/l)	0.54 ± 0.05	0.59 ± 0.05	0.127
hs-CRP (μg/ml)	3.24 ± 0.82	2.44 ± 0.48	0.101
Fibrinogen (mg/ml)	3.83 ± 0.16	3.64 ± 0.18	0.020
Adiponectin (μg/ml)	5.97 ± 0.65	6.63 ± 0.70	0.0013
Placebo			
BMI (kg/m^2)	29.9 ± 0.6	29.7 ± 0.6	0.10
HbA1c (%)	6.25 ± 0.10	6.50 ± 0.12	0.0001
Fasting glucose (mg/dl)	139 ± 3	141 ± 4*	0.30
Fasting insulin (μU/ml)	15.7 ± 1.1**	16.0 ± 1.0	0.29
Total cholesterol (mmol/l)	5.49 ± 0.15	5.56 ± 0.14	0.25
HDL cholesterol (mmol/l)	1.34 ± 0.06**	1.35 ± 0.06	0.39
LDL cholesterol (mmol/l)	3.33 ± 0.14	3.36 ± 0.15	0.28
Triglycerides (mmol/l)	1.79 ± 0.15*	1.94 ± 0.15	0.06
FFA (mmol/l)	0.47 ± 0.03	0.55 ± 0.04	0.017
hs-CRP (μg/ml)	2.32 ± 0.24	2.25 ± 0.37	0.09
Fibrinogen (mg/ml)	3.83 ± 0.13	3.82 ± 0.12	0.49
Adiponectin (μg/ml)	9.45 ± 0.66***	9.73 ± 0.66***	0.26

FFA free fatty acids; HbA1c, haemoglobin A1c; hs-CRP high-sensitivity C-reactive protein.
Comparison with Caiapo group: *$p < 0.03$, **$p < 0.04$, ***$p < 0.002$; all other $p > 0.08$.

the Medgenix immunoenzymetric assay (Biosource Europe S.A., Nivelles, Belgium; ICV 7.5%). HbA1c was measured by high-performance liquid chromatography on a Variant II analyser (BioRad Laboratories, München, Germany; ICV 1.7%). Total triglycerides (TG) and total cholesterol (TC) were measured by enzyme colorimetric assays on an analyser Express Plus (Bayer Vital; interassay: TG ICV 3.0%; TC ICV 2.4%). HDL cholesterol was analysed by precipitation with dextran sulphate and determined analogously to TC (ICV 5.8%). LDL-cholesterol was calculated by using the Friedewald formula (LDL-cholesterol = total cholesterol − triglycerides/5 − HDL cholesterol). FFA were determined by a modified enzyme colorimetric assay (Roche Diagnostics, Mannheim, Germany; ICV 7.9%). Adiponectin was analysed by radioimmunoassay (LINCO Research, St Charles, MO, USA), fibrinogen by nephelometry (Dade Behring, Marburg, Germany) and hs-CRP by immunturbidimetry (Roche/Hitachi Analyzer, Roche, Mannheim, Germany).

OGTT data were analysed according to the oral glucose insulin sensitivity (OGIS) method [9] as regards insulin sensitivity, which is a glucose insulin model extensively validated against the glucose clamp technique; the insulinogenic index (INI) was used for pancreatic sensitivity to glucose [10] and the disposition index, defined as OGIS × INI, was calculated as an integrated marker of glucose tolerance and beta cell function because it describes the interrelationships between the mechanisms that regulate insulin secretion when insulin sensitivity changes [11]. The areas under the curves (AUC) were calculated by integrating (trapezoidal rule) the concentration time courses. All data and results are reported as mean ± s.e.m. The effects of the treatment on the concentrations of outcome parameters were analysed by two-way analysis of covariance for repeated measurements (ANCOVA); also Student's *t*-test was used when appropriate after log-transformation of the variables to ensure normality. As OGTT reproducibility has previously been questioned at least in the context of diabetes screening [12], OGTT-derived results have also been analysed by comparing the differences of baseline and final visit between the two groups in order to reduce the variability. Multiple linear regressions were used to assess correlation between parameters (log of

the relative change from baseline to final visit). A p value of <0.05 was considered statistically significant.

Results

Metabolic Control

Table 1 shows the changes of the metabolic parameters before and after 5 months of administration of Caiapo or placebo. Following treatment with Caiapo, HbA1c, fasting glucose and triglycerides were significantly reduced, while insulin remained unchanged. Adiponectin increased significantly, fibrinogen decreased, whereas hs-CRP exhibited no significant changes. In the placebo group, no change for any of the parameters between baseline and final visit was observed, except for HbA1c and FFA, which were significantly increased (table 1).

The time courses of glucose and insulin during the OGTT for both groups are shown in figure 1. In the Caiapo group, glucose was significantly reduced at all time points, insulin at 60, 90, 120, and 180 min after treatment. In the placebo group, no data point was significantly different before and after treatment. Following Caiapo, glucose AUC (table 2) was significantly reduced both as total AUC and as dynamic suprabasal AUC ($p = 0.0001$; figure 1). Both total and dynamic ($p = 0.0018$) insulin AUC were reduced at the final visit. A significant increase of insulin sensitivity (OGIS) after Caiapo was observed. OGIS inversely correlated with HbA1c ($r = -0.47$, $p = 0.0003$).

Despite the absolute reduction in insulin concentration, no significant variation of beta cell function was seen. In fact, changes in the INI, which reflects the insulin delivery relative to the prevailing glucose, did not reach statistical significance. The higher OGIS and the relatively stable insulin levels yielded an increased disposition index, meaning an augmented capacity of the beta cell to respond to changes in insulin resistance. As expected after hyperinsulinaemia following glucose administration, FFA during OGTT were inhibited on average by 80% at 120 min (0.11 ± 0.02 mmol/l at baseline and 0.12 ± 0.01 at final visit) and remained low until 3 h. No difference was observed in FFA, either as punctual values or as AUC. Placebo administration did not reveal any significant differences in any of the above parameters (table 2). FFA patterns were very similar to those of Caiapo group, but fasting FFA significantly increased from baseline to final visit (table 1). The analysis of the differences of baseline and final visit between the two groups, which overcomes possible problems because of OGTT variability, confirmed that OGTT parameters, excluding FFA and INI, were ameliorated following Caiapo compared with placebo (table 2).

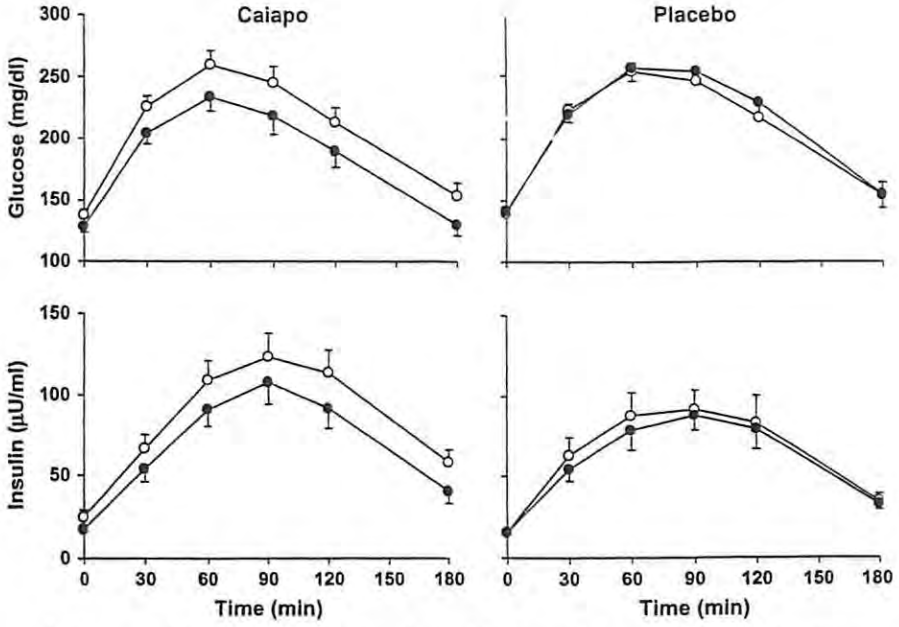

Fig. 1 Time course of glucose and insulin concentration during OGTT in both groups for baseline (open circles) and final visit (closed circles). In the Caiapo group, glucose was significantly reduced at time 0 ($p = 0.033$) and at 30, 60, 90, 120 and 180 min ($p < 0.0045$). No significant difference was detected for fasting insulin, while it was lower at final visit during the dynamic part of the test (p 0.003–0.048). In the placebo group, no significant difference was detected at any data point.

Table 2 Metabolic and lipid parameters during OGTT and between-group comparison, at baseline and after 5 months of Caiapo or placebo (final visit)

Parameter		Baseline	Final visit	P value (baseline vs. final)	Mean change ± s.e.	Between-group difference	P value
Glucose AUC (g/dl in 180 min)	Placebo	38.63 ± 1.40	39.31 ± 1.50*	0.28	0.68 ± 0.83	−4.85 ± 1.33	0.0001
	Caiapo	38.16 ± 1.69	33.99 ± 1.75	0.0001	−4.17 ± 1.04		
Insulin AUC (mU/ml in 180 min)	Placebo	12.43 ± 1.97	11.44 ± 1.48	0.25	−0.99 ± 0.79	−2.16 ± 1.31	0.013
	Caiapo	16.19 ± 1.74	13.03 ± 1.48	0.0007	−3.16 ± 1.04		
FFA AUC (mmol/l in 180 min)	Placebo	42.7 ± 2.7	47.9 ± 3.5	0.082	5.1 ± 3.6	−1.0 ± 5.0	0.932
	Caiapo	45.2 ± 4.1	49.4 ± 4.0	0.088	4.2 ± 3.6		
OGIS (ml/m^2/min)	Placebo	307 ± 10	313 ± 10	0.167	6 ± 7	22 ± 14	0.034
	Caiapo	293 ± 15	321 ± 12	0.0072	28 ± 12		
Insulinogenic Index ($\mu U_{INS}/mg_{GLUC}$)	Placebo	83 ± 13	68 ± 16**	0.17	−15 ± 10	47 ± 25	0.081
	Caiapo	111 ± 20	143 ± 36	0.16	32 ± 23		
Disposition Index (common units)	Placebo	243 ± 32	189 ± 43*	0.23	−54 ± 39	180 ± 79	0.026
	Caiapo	300 ± 51	427 ± 100	0.039	127 ± 68		

AUC, area under the curve; FFA, free fatty acids; OGIS, oral glucose insulin sensitivity; OGTT, oral glucose tolerance test.
Comparison with Caiapo group: *$p < 0.02$, **$p < 0.05$; all other $p > 0.07$.

Insulin Sensitivity, Adiponectin and Fibrinogen

Multiple regression between HbA1c vs. randomization status adiponectin and fibrinogen showed that the type of treatment was highly significant ($p = 10^{-7}$), while the covariates adiponectin and fibrinogen did not appear to influence directly HbA1c, but probably only through a secondary effect. No relationship was detected between hs-CRP and OGIS or HbA1c in either cases ($p > 0.2$).

Comparison Between Caiapo and Placebo

At baseline, parameters (tables 1 and 2) and time courses (figure 1) were not different except for insulin at fasting and at 180 min ($p = 0.005$) and for adiponectin, which was lower in the Caiapo group. At the final visit, basal glucose at 90 min ($p = 0.045$) and at 120 min ($p = 0.03$) were lower in the Caiapo group, yielding a lower glucose AUC. The insulinogenic and the disposition indices were higher in the Caiapo group. Adiponectin remained significantly lower in the Caiapo group at the final visit compared with the placebo group. HbA1c at the final visit tended to be more elevated in the placebo group, despite the lower, albeit not significantly different baseline value.

Lipids

No change was observed in cholesterol both within the groups (at baseline and final visit) and between Caiapo and placebo (in terms of TC as well as of HDL and LDL). Mean concentration of TG at baseline was higher in Caiapo than in placebo, while, at the final visit, the absolute values were very similar. In the Caiapo group, there was a significant decrease from baseline of −0.29 ± 0.17 mmol/l, corresponding to −5.7%, while with placebo, TG increased by 0.15 ± 0.13 mmol/l corresponding to +14.4%. Therefore, from baseline to the final visit, TG increased in the placebo and decreased in the Caiapo group, leading to a significant difference at the final visit ($p = 0.0416$).

Tolerability and Safety

A total of 216 adverse events occurred during the study (96 with Caiapo and 120 with placebo), the most frequent being nausea (three subjects), tympanities or diarrhoea (three subjects). Caiapo was indeed well tolerated because side effects rapidly disappeared after 1 week. Safety analysis did not reveal any evidence of toxicity. One subject became pregnant between weeks 16 and 20; pregnancy and delivery were normal.

Discussion

This study confirms the glucose-lowering potency of Caiapo in diet only–treated patients with T2DM over an extended period of time. The improvement of insulin sensitivity was accompanied by increased levels of adiponectin. In addition, we demonstrated a significant decrease in fibrinogen suggesting antiatherosclerotic properties of Caiapo. Caiapo was well tolerated without exhibiting common side effects like weight gain and oedema formation as seen with other insulin-sensitizing compounds such as glitazones.

Following treatment with Caiapo, basal and stimulated glucose levels consistently decreased resulting in a significant drop in HbA1c of 0.21%. When compared with the placebo group, in which HbA1c increased over time, most likely reflecting the natural course of disease, the difference became more pronounced (0.46%). While this improvement seems modest, it should be considered that baseline HbA1c was already low before enrolment into the study, indicating an excellent metabolic control. Amelioration of insulin sensitivity, expressed by increased OGIS, which describes the glucose clearance in relation to insulin levels, was confirmed as the responsible mechanism. Because the glucose clamp as the gold standard for assessment of insulin sensitivity [10] is rather complicated to perform, other indices such as OGIS have been validated against this method. In a recent study, the dynamic OGIS method correlated with peripheral insulin sensitivity assessed by the clamp [13], while fasting measurements are mostly related to hepatic insulin sensitivity. Because in our study also fasting glucose and insulin, the latter not quite statistically significant due to the lower number of subjects than anticipated, were significantly decreased, we suggest that the amelioration of insulin sensitivity involves both liver and skeletal/adipose tissues.

Accordingly, overall glucose tolerance was improved as reflected by the increased disposition index. In good agreement with the increased insulin sensitivity, we could observe a significant decrease in triglyceride levels in the Caiapo group. This was not accompanied by a significant rise in HDL cholesterol most probably because of the small sample size. FFA levels during the OGTT were markedly reduced following glucose administration and the consequent increase of insulin. Following Caiapo treatment, there was an unexplained small, but non-significant increase in FFA levels. Thus, the action of Caiapo on insulin sensitivity does not appear to be mediated through FFA. The fact that fasting FFA increased significantly in the placebo group from baseline to the final visit, while no significant change was observed in Caiapo, could indicate that Caiapo at least seems to prevent FFA increase.

Administration of Caiapo was accompanied by significantly increased levels of adiponectin, which is produced by adipocytes and acts as a modulator of insulin sensitivity. It has been shown that adiponectin levels are low in insulin-resistant states [14] and increase following treatment with compounds that augment insulin sensitivity, such as the glitazones [15]. While the association between the increase in insulin sensitivity and adiponectin is strong and suggestive, we cannot rule out other mechanisms by which Caiapo might improve insulin resistance. Further characterization of a glycopeptide, which has been identified as the substance most likely responsible for the effects of Caiapo [16], will clarify whether Caiapo acts via similar mechanisms as the known insulin sensitizers.

In the present study, fibrinogen, which is involved in atherothrombosis and serves as an indicator of risk for cardiovascular events [17], decreased significantly following Caiapo treatment. Reduction of fibrinogen has been shown to decrease following metformin treatment, which resulted in a reduction in cardiovascular mortality in the United Kingdom Prospective Diabetes Study [18]. As regards hs-CRP, we could find a decrease by 25% in the Caiapo group, which did not reach significance most likely because of the small number of subjects.

Caiapo was well tolerated and no changes in safety parameters such as elevation in liver enzymes or deterioration in kidney function could be observed. The major limitations of this study are the good metabolic control at baseline, which may limit the ability of Caiapo to show a greater effect on HbA1c, as well as the relative small sample size.

In conclusion, the data of this trial reveal an increase in adiponectin associated with the improvement of insulin sensitivity and metabolic control in patients with T2DM following treatment with Caiapo over an extended observation period. Unlike insulin sensitizers such as glitazones, Caiapo does not lead to an increase in body weight or cause oedema. In addition, Caiapo exerts favourable effects on fibrinogen, which is a cardiovascular risk factor. Based on this study, the neutraceutical Caiapo can be considered an effective insulin sensitizer antidiabetic drug with potential anti-atherosclerotic properties but without risk of weight gain and oedema.

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