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The Use of *Cissus quadrangularis* (CQR-300) in the Management of Components of Metabolic Syndrome in Overweight and Obese Participants

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We have previously reported a wide range of components from *Cissus quadrangularis* with *in vitro* effects on lipases and glycosidases. We now report that a preparation of the plant (CQR-300) administered at 300 mg daily was effective in reducing weight, as well as improving blood parameters associated with metabolic syndrome, as well as serotonin levels in obese and overweight individuals.

Keywords: *Cissus quadrangularis*, Vitaceae, CQR-300, Overweight, Obese, Serotonin, Blood lipids.

Metabolic syndrome (MetS) is a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increase the risk of atherosclerotic cardiovascular disease, and all-cause mortality [1]. Worldwide prevalence of MetS has reached epidemic proportions and ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity, socio-economic status) of the population studied, and the definition used [2,3,4]. In fact, MetS, also defined as the clustering of metabolic abnormalities including central obesity, glucose intolerance, dyslipidemia and hypertension, constitutes one of the major causes of morbidity and mortality in the world. Despite the criteria used to define the syndrome, being overweight and obese appear to be important components implicated in the pathophysiology of the disease [5,6,7]. Unfortunately, drug treatment of obesity, despite short-term benefits, is often associated with rebound weight gain after the cessation of drug use, side effects from the medication, and the potential for drug abuse**.** There are, therefore, many studies reported on the use of herbs, vitamins, nutritional supplements, and meal replacement preparations for weight loss as complementary and alternative therapies [8]. However, there is considerable variation in results from use of plant extracts/products in randomized double blind controlled placebo studies due to often unknown chemical compositions, formulations, dose and posology, which affect the efficacy of the therapy [9,10,11].

Extracts and powders of C*issus quadrangularis* L. (Vitaceae, the grape family) have been used for many years to promote bone and tissue healing, as an analgesic, to treat infections, as an anabolic, and to promote weight loss and weight management [12]. A wide variety of chemical constituents have been isolated and identified from it, including steroids, flavonoids, stilbenes, iridoids, triterpenes, β-sitosterol, δ-amyrin, δ-amyrone, and gallic acid derivatives [13,14,15,16]. Based on studies to date, *C. quadrangularis* extracts appear to be exceedingly safe and free from adverse effects at the doses commonly used [12]. In this study we have used the well characterized *C. quadrangularis* product CQR300 (Gateway Health Alliance, Fairfield, CA, USA) containing the same plant material used in our 2007 study [13].

Previous randomized double-blind placebo controlled studies reported on the use of two daily doses of 514 mg each of the *C. quadrangularis* formulation (vs placebo) for 8 weeks, which resulted in significant net reductions in weight and central obesity, as well as in fasting blood glucose, total cholesterol, LDL-cholesterol, triglycerides, and C-reactive protein [17]. In another study, two extract formulations of CQR-300 at doses of 300 and 1028 mg during 8 weeks resulted in a decrease in body weight and body fat as well as in serum lipids and glucose. Also, an increase in plasma HDL-C, 5-HT and creatinine levels was observed [14]. Administration of *C. quadrangularis* in combination with *Irvingia gabonensis* at doses of 300 mg (CQ) and 500 mg (IG), respectively, per day during 10 weeks, resulted in decrease in body weight, body fat percent and waist size in both groups, but the combination group (CQ + IG) resulted in a larger significant decrease in the mean of the weight and significant decrease in plasma cholesterol, LDL-cholesterol and fasting blood glucose levels [18].

Further research on the assessment of the effective dose and an appropriate posology of *C. quandrangularis* is needed and could be of clinical, industrial and socio-economic importance in the treatment of MetS. The aim of this pilot study was, therefore, to test and compare the efficacy of *C. quadrangularis* (CQR300), a standardized extract of *C. quandrangularis*, taken as a daily 300 mg dose, on the reduction of weight and the control of the biochemical parameters of the metabolic syndrome in overweight and obese participants.

The study was an 8-week double blind placebo controlled pilot trial on 61 overweight or obese individuals who were requested to maintain their normal exercise routines and who received individual dietary counseling. Participants were divided into four different groups: Placebo overweight, placebo obese, overweight receiving 300 mg CQR-300 (A); obese receiving 300 mg CQR-300 (B). Anthropometric parameters were measured and blood samples taken every 4 weeks during routine visits.

Effect of CQR-300 on weight loss. Table 1 shows that from the baseline (T0) to week 8 (T8), the obese placebo group, the

overweight group A and the obese group B achieved weight losses of 3.1 ± 1.2%, 8.4 ± 1.1% and 11.3 ± 0.8 respectively. There was also a significant difference (p<0.05) in weight reduction in the obese group from 4 weeks (6.9 ± 0.7) to 8 weeks (10.7 ± 0.7 Kg). However, the reduction was less considerable in the overweight group within the same time interval (variation from 1.7 ± 0.6 Kg to 7.4 ± 1.0 Kg, p< 0.05). The reduction was significant at p < 0.05 at week 4 (T4) and at the end of the study (Week 8; p< 0.01).

Effect of CQR-300 on Body Mass Index The use of CQR-300 revealed a reduction in BMI of 8.4 ± 0.7% in the overweight group A compared with their placebo overweight group; and up to 11.3 ± 1.1 % in the obese group B after 8 weeks (Table 2). After 4 weeks, there was a significant decrease (p < 0.05) in BMI of group B (from 33.8 ± 0.2 to 31.3 ± 0.2), no difference from week 4 to week 8 p > 0.05. It can be observed in Table 2 that reductions in BMI are similar to reduction in body weight in all he groups.

Effect of CQR 300 on waist circumference. Results in Table 3 show up to 11.0 ± 0.9% waist reduction with overweight individuals and 13.1 ± 0.7% with the obese group. There was a general loss in waist circumference observed in all the groups including placebo after 8 weeks. Also, from baseline to week 4, both overweight and obese groups experienced loss in waist circumference which, thereafter, became more consistent in the overweight group (p < 0.05).

Effect of CQR-300 on Hip Circumference. There was a reduction in hip circumference from baseline to week 4 in both overweight and obese groups. The decrease was more consistent in obese group A. As from week 4, CQR300 reduces the hip circumference more in the obese group (13.1 ± 0.6%) than in the overweight group (8.4 ± 0.8%).

Effect of CQR-300 on body fat. In this study, administration of CQR300 reduced body fat from baseline (T0) to week 4 (T4) in both overweight and obese groups. While the reduction continued as from week 4 in the obese group, no change was observed in the overweight group (Table 5).

Effect of CQR-300 on systolic blood pressure. Table 6 shows that although there were slight variations in systolic blood pressure of the placebo groups with time (p>0.05), CQR300 at 300 mg reduced systolic blood pressure both in the obese and overweight groups. However, the reduction was more consistent in the overweight group (7.7 ± 0.6%).

Effect of CQR-300 on diastolic blood pressure. The product was more efficient between baseline (T0) and week 4 (T4) in both the overweight and obese groups, as observed in Table 7. However, the reduction was more consistent in the overweight group A than the obese group B after week 8 (16.7 ± 0.8%).

In all following Tables values are means ± sem. For the same row, values with different letters (a, b, c) are significantly different at p < 0.05. Values at T0, T4, and T8 were compared with ANOVA followed by a post-hoc test. Comparison of differences between T0-T4 and T0-T8 were made using Paired student's t test.

Table 1: Effect of CQR300 dose on body weight after 8 weeks treatment.

	Body Weight (Kg)					
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 – T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	80.9 ± 1.1^{a}	81.3 ± 1.2^{a}	81.2 ± 1.5^{a}	-0.4 ± 0.4^{a}	-0.3 ± 0.8^{a}	0.4 ± 1.0
Placebo Obese	85.4 ± 0.1^{a}	83.2 ± 0.8^{ab}	82.8 ±1.1^{b}	2.2 ± 0.7^{a}	2.6 ± 1.0^{a}	-3.1 ± 1.2
Overweight group (A)	87.9 ± 0.3^{a}	86.2 ± 0.5^{a}	80.5 ± 0.8^{b}	1.7 ± 0.6^{a}	7.4 ± 1.0^{b}	-8.4 ± 1.1
Obese group (B)	94.2 ± 0.3^{a}	87.3 ± 0.8^{b}	83.5 ± 0.8^{b}	6.9 ± 0.7^{a}	10.7 ± 0.7^{b}	-11.3 ± 0.8

Table 2: Effect of CQR300 dose on body mass index after 8 weeks treatment.

	Body Mass Index (Kg/m^2)					
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	28.0 ± 0.5^{a}	28.1 ± 0.5^{a}	28.1 ± 0.5^{a}	-0.1 ± 0.2^{a}	-0.1 ± 0.3^{a}	0.4 ± 1.0
Placebo Obese	30.5 ± 0.1^{a}	29.7 ± 0.3^{ab}	29.6 ± 0.4^{b}	0.8 ± 0.3^{a}	0.9 ± 0.4^{a}	-3.1 ± 1.2
Overweight group (A)	28.3 ± 0.1^{a}	27.8 ± 0.2^{a}	25.9 ± 0.2^{b}	0.5 ± 0.2^{a}	2.4 ± 0.2^{b}	-8.4 ± 0.7
Obese group (B)	33.8 ± 0.2^{a}	31.3 ± 0.2^{b}	30.0 ± 0.3^{b}	2.5 ± 0.2^{a}	3.8 ± 0.3^{b}	-11.3 ± 1.1

Table 3: Effect of CQR300 dose on waist circumference after 8 weeks treatment.

	Waist Circumference (cm)					
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	93.9 ± 1.2^{a}	93.5 ± 1.2^{a}	93.1 ± 1.4^{a}	0.4 ± 0.4^{a}	0.8 ± 0.8^{a}	-0.9 ± 0.8
Placebo Obese	98.4 ± 0.1^{a}	95.4 ± 0.8^{ab}	94.7 ± 1.1^{b}	3.0 ± 0.8^{a}	3.7 ± 1.0^{a}	-3.8 ± 1.0
Overweight group (A)	99.9 ± 0.3^{a}	96.7 ± 0.5^{b}	88.9 ± 0.7^{c}	3.2 ± 0.6^{a}	11.0 ± 0.9^{b}	-11.0 ± 0.9
Obese group (B)	104.2 ± 0.3^{a}	95.8 ± 0.8^{b}	90.5 ± 0.8^{c}	8.4 ± 0.7^{a}	13.7 ± 0.7^{b}	-13.1 ± 0.7

Table 4: Effect of CQR300 dose on hip circumference after 8 weeks treatment

	Hip Circumference (cm)					
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	114.5 ± 1.6^{a}	111.7 ± 1.2^{a}	112.0 ± 1.5^{a}	2.8 ± 2.1^{a}	2.5 ± 2.3^{a}	-1.9 ± 2.1
Placebo Obese	116.7 ± 2.1^{a}	113.6 ± 0.8^{a}	113.6 ± 1.1^{a}	3.1 ± 2.0^{a}	3.1 ± 2.0^{a}	-2.5 ± 1.7
Overweight group (A)	118.5 ± 0.3^{a}	115.7 ± 0.5^{b}	108.5 ± 0.7^{c}	2.8 ± 0.6^{a}	10.0 ± 0.9^{b}	-8.4 ± 0.8
Obese group (B)	119.3 ± 0.3^{a}	110.1 ± 0.8^{b}	103.7 ± 0.8^{c}	9.2 ± 0.7^{a}	15.6 ± 0.7^{b}	-13.1 ± 0.6

Table 5: Effect of CQR300 dose on body fat after 8 weeks treatment

	Body Fat (%)					
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	43.1 ± 1.2^{a}	42.9 ± 1.2^{a}	43.0 ± 1.5^{a}	0.2 ± 1.3^{a}	0.1 ± 1.5^{a}	0.1 ± 3.5
Placebo Obese	44.9 ± 1.6^{a}	45.0 ± 0.9^{a}	44.7 ± 1.0^{a}	-0.1 ± 1.5^{a}	0.1 ± 1.6^{a}	0.3 ± 3.5
Overweight group (A)	43.7 ± 0.7^{a}	32.2 ± 0.5^{b}	29.5 ± 0.7^{b}	11.5 ± 0.8^{a}	14.2 ± 1.0^{b}	-32.1 ± 2.0
Obese group (B)	45.6 ± 0.5^{a}	38.1 ± 0.8^{b}	33.7 ± 0.9c	7.5 ± 0.7^{a}	11.9 ± 0.7^{b}	-26.1 ± 1.6

Table 6: Effect of CQR300 dose on systolic blood pressure after 8 weeks treatment.

Systolic blood pressure (mmHg)						
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	134.45 ± 1.62 [a]	131.9 ± 1.2[a]	132.0 ± 1.5[a]	2.5 ± 2.1 [a]	2.5 ± 2.3 [a]	-1.7 ± 1.8
Placebo Obese	136.71 ± 2.10 [a]	134.0 ± 0.9[a]	133.6 ± 1.1[a]	2.7 ± 2.0 [a]	3.1 ± 1.8 [a]	-2.2 ± 1.3
Overweight group (A)	137.65 ± 0.40 [a]	131.2 ± 0.5[b]	127.0 ± 0.1c	6.5 ± 0.6 [a]	10.7 ± 0.9 [b]	-7.7 ± 0.6
Obese group (B)	140.70 ± 0.43 [a]	135.1 ± 0.8[b]	131.7 ± 0.9[b]	5.7 ± 0.6 [a]	9.0 ± 0.7 [b]	-6.4 ± 0.5

Table 7: Effect of CQR300 dose on diastolic blood pressure after 8 weeks treatment

Diastolic blood pressure (mmHg)						
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	86.1 ± 1.1[a]	83.9 ± 1.2 [a]	85.0 ± 1.5[a]	2.2 ± 1.3 [a]	1.1 ± 1.5 [a]	-1.2 ± 1.8
Placebo Obese	87.9 ± 1.6[a]	86.0 ± 0.9[a]	86.7 ± 1.0[a]	1.9 ± 1.5 [a]	1.1 ± 1.6 [a]	-1.1 ± 1.8
Overweight group (A)	90.7 ± 0.4[a]	79.2 ± 0.5[b]	75.5 ± 0.7c	11.5 ± 0.5 [a]	15.2 ± 0.8 [b]	-16.7 ± 0.8
Obese group (B)	88.7 ± 0.4[a]	82.1 ± 0.8[b]	79.7 ± 0.9[b]	6.7 ± 0.7 [a]	9.0 ± 0.7 [b]	-10.2 ± 0.8

Table 8: Effect of CQR300 dose on total cholesterol after 8 weeks treatment

Total Cholesterol (mg/dL)						
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	199.8 ± 1.2[a]	182.5 ± 2.1 [b]	184.3 ± 3.0 [b]	17.3 ± 2.3 [a]	15.5 ± 3.3 [a]	-7.7 ± 1.7
Placebo Obese	201.4 ± 4.2[a]	193.1 ± 1.7[b]	191.1 ± 3.0[b]	8.3 ± 1.9 [a]	10.3 ± 4.4 [a]	-5.0 ± 2.1
Overweight group (A)	190.0 ± 0.7[a]	160.5 ± 3.3[b]	130.0 ± 2.8c	29.5 ± 3.4 [a]	60.1 ± 2.9 [b*]	-31.6 ± 1.5
Obese group (B)	200.1 ± 2.1[a]	175.5 ± 0.9[b]	179.412 ± 3.1[b]	24.5 ± 2.1 [a]	20.7 ± 3.3 [a]	-10.2 ± 1.6

*p<0.01

Table 9: Effect of CQR300 dose on triglycerides after 8 weeks treatment

Triglycerides (mg/dL)						
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	131.2 ± 2.5[a]	132.6 ± 2.8[a]	133.5 ± 2.5[a]	-1.4 ± 3.0 [a]	-2.3 ± 2.2 [a]	1.9 ± 1.7
Placebo Obese	135.0 ± 2.3[a]	126.2 ± 5.2[a]	129.3 ± 3.2[a]	8.8 ± 3.4 [a]	5.7 ± 2.2 [a]	-4.2 ± 1.6
Overweight group (A)	119.2 ± 2.3[a]	98.6 ± 2.4[b]	84.8 ± 0.7[c]	20.6 ± 2.8 [a]	34.4 ± 2.5 [b]	-28.3 ± 1.7
Obese group (B)	135.7 ± 1.8[a]	118.5 ± 5.9[b]	118.0 ± 2.5[b]	17.1 ± 5.4 [a]	17.6 ± 2.9 [a]	-12.8 ± 2.0

Table 10: Effect of CQR300 dose on HDL-cholesterol after 8 weeks treatment

HDL-Cholesterol (mg/dL)						
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	32.0 ± 1.2[a]	36.0 ± 1.2[a]	36.0 ± 1.5[a]	-4.0 ± 1.3 [a]	-4.0 ± 1.6 [a]	13.6 ± 5.0
Placebo Obese	28.0 ± 1.6[a]	32.0 ± 1.0[b]	34.1 ± 1.0[b]	-4.0 ± 1.6 [a]	-6.1 ± 1.5 [a]	23.5 ± 6.4
Overweight group (A)	34.0 ± 0.7[a]	40.7 ± 1.4[b]	45.7 ± 1.0[b]	-6.7 ± 1.4 [a]	-11.6 ± 1.2 [b]	35.2 ± 3.9
Obese group (B)	31.7 ± 1.1[a]	34.7 ± 1.4[ab]	37.8 ± 1.0[b]	-3.0 ± 1.5 [a]	-6.2 ± 1.5 [a]	22.4 ± 5.4

Table 11: Effect of CQR300 dose on fasting blood glucose after 8 weeks treatment

Fasting blood Glucose (mg/dL)						
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	4.0 ± 0.3[a]	4.0 ± 0.1[a]	3.8 ± 0.2[a]	0.1 ± 0.2 [a]	0.2 ± 0.3 [a]	-1.5 ± 8.3
Placebo Obese	4.5 ± 0.3[a]	4.3 ± 0.1[a]	4.3 ± 0.3[a]	0.2 ± 0.3 [a]	0.2 ± 0.3 [a]	-3.8 ± 6.5
Overweight group (A)	3.9 ± 0.2[a]	3.5 ± 0.2[ab]	3.3 ± 0.2[b]	0.4 ± 0.1 [a]	0.6 ± 0.2 [a]	-14.2 ± 4.2
Obese group (B)	4.8 ± 0.3 [a]	4.2 ± 0.3[a]	4.1 ± 0.2[a]	0.6 ± 0.1 [a]	0.7 ± 0.2 [a]	-12.8 ± 4.5

Table 12: Effect of CQR300 dose on serotonin levels

Serotonin µg/L						
Groups	**Initial (T0)**	**Week 4 (T4)**	**Week 8 (T8)**	**T0 - T4**	**T0 - T8**	**% change after 8 weeks**
Placebo Overweight	2.7 ± 0.3[a]	2.7 ± 0.1[a]	2.4 ± 0.2[a]	-0.0 ± 0.2 [a]	0.3 ± 0.3 [a]	-0.3 ± 15.2
Placebo Obese	2.5 ± 0.3[a]	2.5 ± 0.3[a]	2.3 ± 0.2[a]	0.1 ± 0.4 [a]	0.2 ± 0.3 [a]	-0.2 ± 14.7
Overweight group (A)	2.7 ± 0.2[a]	3.7 ± 0.3[b]	5.3 ± 0.3[c]	-1.0 ± 0.7 [a]	-2.6 ± 0.9 [b]	115.7 ± 43.1
Obese group (B)	3.1 ± 0.3[a]	3.6 ± 0.3[b]	3.8 ± 0.2[c]	-0.5 ± 0.2 [a]	-0.8 ± 0.2 [a]	34.2 ± 9.6

Effect of CQR300 on total cholesterol. As shown in Table 8, there was an important reduction of up to 31.6 ± 1.5% in the overweight group A. Compared with the placebo, there were also significant decreases in total cholesterol after 4 weeks (p<0.05) and 8 weeks (p<0.01) for the overweight, but not the obese group.

Effect of CQR-300 on triglycerides. CQR300 decreased triglyceride levels (p<0.05) from baseline (T0) to week 4 in both overweight and obese groups. As from week 4, triglycerides further decreased significantly (p<0.05) in the overweight group, but not in the obese participants on CQR-300 (Table 9).

Effect of CQR300 on HDL-cholesterol. As shown in Table 10, CQR300 significantly (p < 0.05) increased the level of HDL-cholesterol in the overweight group (A) from baseline to week 4 (p<0.05), but the significant increase was observed in the obese group (B) only at week 8.

Effect of CQR-300 on fasting blood glucose. There was a reduction in blood glucose, but it was not significant in either groups A and B at week 4. CQR300 did significantly reduce blood glucose at week 8, but only in the overweight group (Table 11). Slight variations were observed with placebo groups, although not significant.

Effect Of CQR-300 on serotonin levels. Administration of CQR300 gradually increased serotonin levels from baseline, week 4, to week 8, as shown in Table 12. Differences in variations from week 4 to week 8 were only significant in the overweight group. CQR300 in the obese group increased serotonin levels to up to 115.7 ± 43.1 %.

The ability of *Cissus quadrangularis* extracts to reduce weight has been confirmed. This activity might be due to its ability to inhibit key enzymes of metabolism such as pancreatic lipase, α-amylase, and α-glucosidase *in vitro*, all of which could contribute to weight reduction. This double blind placebo controlled study gave a reduction in weight of 11.3 ± 0.8% in the obese group (B) and 8.4 ± 1.1% in the overweight group (A) compared with placebo groups after the 8 weeks of the trial (Table 1). Similar results were obtained in 2008 with a reduction in weight of 7.5% in an obese group receiving CQR-300 (150 mg twice daily) [18].

Several other randomized, double-blind placebo-controlled studies of the same design have demonstrated good, but lower weight reduction among overweight and obese participants. A study with *C. quadrangularis* formulation Cylaris™ showed that participants who received two daily doses (514 mg each) of the formulation or placebo for 8 weeks obtained reductions in body weight of 6.9% in an obese group and 4.9% in an overweight group with no restriction in diet [17]. Despite the fact that the dose they used was greater than CQR-300 in groups A and B, the present study showed a better reduction and confirms CQR-300 as a good extract for the management of body weight in metabolic syndrome. Cylaris™ has a greater complexity in composition (contains *Glycine max* extract, *Camellia sinensis* extract and ChromeMate™), which may have reduced the efficacy. A study conducted on another *C. quadrangularis* product, Lepticore™, demonstrated weight loss of 5.4% obtained at a single dose (300 mg, Formula A) and 6.95% with Formula B (300 mg, twice daily). LeptiCore®, a proprietary blend of plant-based polysaccharides, esterified fatty acids, pomegranate, polyphenols, ellagic acid, beta carotene, and *Aphanizomenon flosaquae* extract, again showed less weight loss, despite the extra components [11].

Our study also showed a reduction in BMI of 8.4 ± 0.7% in the overweight group A compared with their placebo and up to 11.3 ± 1.1 % in obese participants (Group B) after 8 weeks and at a single daily dose of 300 mg CQR-300, as shown in Table 2. The reduction in BMI seen here is greater than that with the formulation Cylaris™ [17]. Waist circumference is an extremely important determinant in the diagnosis of obesity and metabolic syndrome [4]. This study revealed (Table 3) an important reduction in waist and hip circumferences. Up to 11.0 ± 0.9% reduction in waist circumference was observed with overweight individuals (group A) and 13.1 ± 0.7% with the obese (B). The reduction in waist circumference both in overweight and obese individuals in this study was accompanied, as shown in Table 4, with a subsequent reduction in hip circumference 8.4 ± 0.8% and 13.1 ± 0.6% respectively for overweight (group A) and obese individuals (Group B). This result suggests that the WHO criterion for the definition and diagnosis of MetS, which uses the waist to hip ratio could be the best criterion to assess the efficacy of treatment with CQR-300.

Previous studies have reported that the supplemented extract of *C. quadrangularis* can reduce body fat [14,17]. The present study confirms the efficacy of *C. quadrangularis* at 300 mg because fat loss of 32.1 ± 2.0% was observed in the overweight group (A) and even greater than the 26.1 ± 1.6% observed in the obese group B.

CQR-300 reduced both systolic (Table 6) and diastolic blood pressure (Table 7). With the diastolic, there was a more considerable reduction in the overweight group A (16.7 ± 0.8%) than the obese group B (10.2 ± 0.8%). The same profile was observed with the reduction in systolic blood pressure in the overweight (7.7 ± 0.6 %) and obese groups (6.4 ± 0.5%). The effect of dose and posology influence the reduction. The reduction of hemodynamic factors may be due to the presence of agents promoting vasodilation through interactions with the renin angiotensin system (RAS), and reduction of blood glucose; regulating expression of angiotensinogen, angiotensin II (AT II), and the AT1 receptor [19]. CQR-300 may also act through direct action on adipocytes recently demonstrated to produce aldosterone also [4].

From Table 8 it can be seen that were significant decreases in total cholesterol after 4 weeks ($p<0.05$) and 8 weeks ($p<0.01$) for the overweight, but not the obese group. Triglyceride (Table 9) and fasting blood glucose levels (Table 11) were also significantly ($p< 0.05$) reduced in the overweight, but not the obese participants on CQR-300. Previous studies reported that for obese participants on a restricted diet, six weeks use of CQR-300 (150 mg, twice daily) reduced plasma total cholesterol by 18.0%, LDL-cholesterol by 29.0%, triacylglycerol by 21.7%, fasting blood glucose by 14.6% and increased the concentration of HDL-cholesterol by 21.1% [14]. The reduction of triglycerides in the obese group is lower in this study compared with the 21.7% obtained at 6 weeks at the dose of 150 mg twice daily [14]. CQR-300 improved the levels of HDL-cholesterol more in the overweight group (35.2 ± 3.9%) than in the obese group (22.4 ± 5.4%), even though, surprisingly, both placebo controlled groups also had their HDL-C values increased (Table 10). This result is in accordance with a reduction of 21% obtained with a dose of 150 mg twice daily, despite the shorter duration of the experiment and the restriction in diet to 2100 kcal/day [14]. The study also suggests the ability of CQR-300 to reduce the incidence of diabetes. In fact, as shown in Table 11, CQR-300 led to the reduction of blood glucose (14.23 ± 4.15%) in the overweight group with less difference in the obese group B at week 8 (change from 3.9 ± 0.2 to 3.3 ± 0.2, $p< 0.05$).

Arnold *et al.* [20] showed that serotonin affects eating behavior and body weight, and that increased serotonin plasma levels are associated with decreased food intake, reduced weight gain, and increased energy expenditure. In Table 12, serotonin levels significantly increased at 4 weeks ($p<0.05$) and 8 weeks ($p<0.01$) at about 3.4 times in the overweight group (115.7 ± 43.1%), but less in the obese group (34.2 ± 9.6%) compared with the placebo groups. The single dose of 300 mg of CQR-300 demonstrated more activity in serotonin production than the same single dose of Lepticore™ (28.6%) [11]. *C. quadrangularis* phytosterols and fiber extracts have been shown to have anti-lipase, and anorexiant properties that reduce the absorption of dietary fats and enhance satiation by increasing serum serotonin levels [17]. Administration of CQR-300 twice daily seems to promote production of serotonin compared with a single 300 mg dose in group B.

In the 2006 study [17] on an overweight group with no diet restriction, a Cylaris™ formulation of 514 mg twice daily administration led to a reduction of 18.8% of total cholesterol, an increase of 19.6% in HDL-C levels, a decrease in triglycerides of 15.0% and a reduction of 11.4% in fasting blood glucose. Although both CQR-300 and Cylaris™ were administered twice daily, but at different doses, CQR-300 has been demonstrated to be more active in the overweight group compared with Cylaris™, despite the more complex formulation of the latter [21]. CQR-300 in the overweight group improved HDL-C (28.3%) and better than the 514 mg Cylaris™ (19.6%) [17]. Compared with another randomized double blind placebo controlled study [18] in an obese (generally considered as a disease) group after 8 weeks, CQR-300 (150 mg twice daily), demonstrated a reduction of 22.6% total cholesterol, better than those obtained in this study. They also observed a

reduction of 12.5% in fasting blood glucose. A similar reduction was obtained in this study (Table 11), although not significant.

CQR300 like other plant extracts/plant-based formulations in various randomized double-blind placebo controlled studies showed effectiveness for treatment at different doses on individual components of metabolic syndrome. Boozer *et al*. [22] administered a herbal supplement: (Guarana and other components with 72 mg Ephedra, 240 mg caffeine) during 8 weeks on overweight participants and observed a significant decrease in body weight, total body fat, reduction in hip & waist circumference, reduction in serum TG (23%) compared with a placebo group. Greenway *et al.* [10] working on a herbal supplement containing caffeine (210 mg) and Ephedra (72 mg) administered over 12 weeks to obese and overweight subjects observed a significant decrease in body weight and the percentage of fat, but no differences in lipid levels, or blood pressure compared with placebo. Use of Ephedra though is not without possible danger.

Several studies underline [1,4,23] the difficulty to manage MetS clinically, because there is no recognized method to prevent or improve the whole syndrome. CQR-300 seems to be a very good option given the efficacy mainly in overweight people at a dose of 150 mg, twice daily, to reduce body weight, primary anthropometric measurements, blood pressure, blood glucose, total cholesterol, and to increase HDL-cholesterol and serotonin levels.

Summary of results: After 8 weeks of treatment, overweight participants of the placebo group showed a slight increase, while the obese participants showed a 3.1% decrease in body weight. In the same time period, there was an 8.4 and 11.3 % decrease in the body weight respectively of overweight and obese participants on CQR-300. The decrease in weight in the CQR-300 group was paralleled by a significant decrease in the waist and hip circumferences (p<0.05), systolic and diastolic blood pressures (p<0.05). Compared with the placebo, there were also significant decreases in total cholesterol after 4 weeks (p<0.05) and 8 weeks (p<0.01) for the overweight but not the obese group. Triglyceride and fasting blood glucose levels were also significantly (p<0.005) reduced in overweight but not obese participants on CQR-300. On the other hand, significant increases in serotonin levels were observed at 4 weeks (p<0.05) and 8 weeks (p<0.01).

Experimental

Participants and methods: A total of 61 overweight and obese participants (24 males and 37 females) aged between 19 and 55 years were selected from a group responding to a radio advertisement. The radio advert mentioned the potential weight reducing benefit of the study and normal weight participants did not present themselves. After physical examination and laboratory screening tests, diabetics, and pregnant and lactating women were excluded. None of these patients took any weight reducing drugs and none was following any specific diet. The purpose, nature and potential risks of the study were explained to all patients and written informed consent was obtained before their participation. The experimental protocol was approved by the local research ethics committee.

Study design: The 8-week intervention was designed as a randomized, double blind, placebo-controlled, crossover study. Participants were initially separated into 2 groups [overweight (A) and obese (B)] based on their BMI. They were given either the active formulation (300 mg CQR-300) or corn starch capsules (placebo). The placebo capsules, as well as those of the CQR300 formulation (a proprietary extract of *Cissus quadrangularis*), were obtained from Gateway Health Alliance, Fairfield, CA, USA, and were identical in shape, color and appearance, and neither the participant nor the researchers knew in which group the participants had been registered. Participants received 300 mg capsules per day as a single dose, 30 min before their main (mid-day) meal and were examined every week. During these visits their body weight, body fat, waist and hip circumferences were recorded. Subjective findings such as increased or decreased appetite, feeling of lightness and gastrointestinal pains were individually solicited and noted. Side effects of the formulations, if any, were noted. The participants were also interviewed about their physical activity and food intake during the study period. They were asked to keep a record of their food intake over 7 consecutive days (using household measurements). At the start of the study, as well as on weeks 4 and 8, blood was collected and plasma prepared and stored at -70^{o}C.

Anthropometric measurements: These were collected weekly. Body weight and body fat were measured using a TANITA monitor Scale, after an overnight fast, and with participants wearing light clothing. Waist and hip circumferences were measured using soft non- stretchable plastic tape on the narrowest and the widest parts of the trunk.

Blood pressure measurements: These were taken weekly using a mercury sphygmomanometer. On each occasion at least 2 readings were taken and the mean value recorded. An appropriate adult cuff was applied 2 to 3 cm above the antecubital fossa of the right arm. Blood pressure was measured to the nearest 2 mm Hg, reading the calibration below the meniscus with the participant in a sitting position.

Blood sample collection and treatment: Fasting venous blood (5 mL) was collected from participants into heparinized tubes. After centrifugation at 4500 *g* for 10 min at 4^{0}C, plasma was collected and stored at –70^{o}C until analysis.

Biochemical analysis of plasma: Total cholesterol in plasma was determined using an enzymatic method, while plasma triglyceride was determined as previously described [11]. HDL cholesterol was determined using a heparin manganese precipitation of Apo B-containing lipoproteins. Blood glucose was determined using the glucose oxidase method and serotonin by an ELISA kit supplied by IBL International GmbH, Germany.

Statistical analyses: These were made using the statistical package for social sciences (SPSS) Windows version 17.0. Results are expressed as means ± SEM. One way analysis of variance (ANOVA) was used to compare continuous variables followed by post hoc LSD. Paired Student's t test was carried out on the start and end values and also on the differences between the placebo and the active formulation effect on body weight change.

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