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Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Preliminary study

F. DI PIERRO[1], A. BRESSAN[2], D. RANALDI[3], G. RAPACIOLI[4], L. GIACOMELLI[5], A. BERTUCCIOLI[6]

[1]Velleja Research, Milan, Italy; [2]A.S.U.R. Area 1, Pesaro, Italy; [3]Biologist Consultant, Pharmextracta, Pontenure; [4]A.I.O.R., Piacenza, Italy; [5]Department of Surgical Sciences and Integrated Diagnostics, School of Medicine, Genova University; [6]AIFeM, Ravenna, Italy

Abstract. – OBJECTIVE: This randomized, controlled study aims to evaluate the tolerability and the efficacy of curcumin in overweight subjects affected from metabolic syndrome, with a focus on impaired glucose intolerance and android-type fat accumulation.

PATIENTS AND METHODS: Forty-four subjects, selected among those who after 30 days of diet and intervention lifestyle have shown a weight loss < 2%, have been treated for further 30 days either with curcumin complexed with phosphatidylserine in phytosome form or with pure phosphatidylserine. Outcomes concerning anthropometric measurements and body composition were analyzed at enrollment and after 30 and 60 days.

RESULTS: Curcumin administration increased weight loss from 1.88 to 4.91%, enhanced percentage reduction of body fat (from 0.70 to 8.43%), increased waistline reduction (from 2.36 to 4.14%), improved hip circumference reduction from 0.74 to 2.51% and enhanced reduction of BMI (from 2.10 to 6.43%) ($p < 0.01$ for all comparisons). Phosphatidylserine did not show any statistical significant effect. Tolerability was very good for both treatments, and no drop-out was reported.

CONCLUSIONS: Although preliminary, our findings suggest that a bioavailable form of curcumin is well-tolerated and can positively influence weight management in overweight people.

Key Words:
Curcumin phytosome, Phosphatidylserine, White adipose tissue.

Introduction

Metabolic syndrome, along with diabetes mellitus and obesity, is rapidly increasing in Western world due to negative lifestyle habits which favor fat and sugar-based meals, as well as low levels of physical activity[1]. Being mainly characterized by central obesity, high blood pressure, high triglycerides, low HDL-cholesterol and insulin-resistance, metabolic syndrome is an important risk factor for cancer and cardio-metabolic diseases[2,3]. Pharmacological intervention in obese and metabolic syndrome patients is taken into consideration when diet[4] and physical exercise[5] are not sufficient to achieve a successful control. However, this therapeutic strategy remains controversial since its long-term efficacy is modest and some concerns about safety exist[6].

Among the different metabolic abnormalities, visceral fat represents a very important feature of metabolic syndrome. It is a dynamic endocrine organ that secretes mediators and inflammatory cytokines also known as adipokines. Their dysregulation supports abdominal obesity and represents a causal factor mediating insulin resistance[7]. Indeed, drugs counteracting insulin resistance can reduce central obesity.[8,9]. In addition, cortisol is another important factor promoting metabolic syndrome[10]. Cortisol can be indeed increased in visceral fat by the action of 11-beta-hydroxysteroid dehydrogenase type 1 (11-βHSD1). This enzyme is highly expressed in liver and adipose tissue. It physiologically reduces the inactive hormone cortisone into its active form cortisol[11]. Overexpression of the 11-βHSD1 gene in adipocytes is related with high cortisol concentrations in adipose tissue and with development of central obesity, insulin-resistance, and diabetes in murine models[12]. On the other hand,

Corresponding Author: Francesco Di Pierro, MD; e-mail: f.dipierro@vellejaresearch.com

11-βHSD1 knockout mice exposed to a high-fat diet are protected against the development of obesity and hyperglycemia[13]. Moreover, 11-βHSD1 inhibitors have been shown to be effective in treating diabetes and other different aspects of metabolic syndrome promoting weight loss and reducing insulin-resistance and hyperglycemia in humans[14-16].

Curcumin is a bis-α, β-unsaturated diketone, commonly called diferuloylmethane. Along with demethoxycurcumin and bisdemethoxycurcumin, curcumin constitutes the group of curcuminoids of the rhizome extract of *Curcuma longa*[17]. It is endowed with a wide spectrum of pharmacological activities with potential relevance for the treatment of metabolic syndrome, obesity and diabetes. In human adipose tissue, curcumin reduces the expression of the potent pro-inflammatory adipokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), and induces the expression of adiponectin, the most important anti-inflammatory agent secreted by adipocytes[18,19]. Curcumin presents anti-hyperglycemic and insulin sensitizer effects[20] and when administered in a pre-diabetic population significantly reduces the number of individuals who eventually developed type-2 diabetes and appears to improve overall function of β-cells[21]. Moreover, curcumin is selective inhibitor of human 11-βHSD1[22].

On this basis, we have evaluated the clinical effect of curcumin in obese patients affected from metabolic syndrome, with a focus on its impact on weight and waistline. In consideration of some very well-known curcumin problems, like chemical instability at intestinal pH, very poor water solubility, bad oral bioavailability and high rate of urine elimination as glucuronide or sulfate curcumin[23,17] we have tested the curcumin in form of phytosome and in presence of piperine. The phytosome technology creates intermolecular bonding between curcumin and one or more phospholipid molecules stabilizing curcumin and make it highly bioavailable both in rats and in humans[24,25] whilst the presence of piperine reduces the curcumin conjugation process and then its rapid urinary elimination[26].

Patients and Methods

Study Criteria

This 2-month, randomized, controlled clinical trial was conducted in a clinical practice setting, in accordance with the principles of the Declaration of Helsinki and consistent with Good Clinical Practice, as defined by the International Conference on Harmonization, and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The protocol and subject consent and privacy forms were approved by the Review Board before the initiation of the study.

This study was conducted in a single center in Italy between April 2012 and April 2013. Forty-four adults (18-70 years), Caucasian, overweight patients with body mass index (BMI) between 25.0 and 29.9, diagnosed with metabolic syndrome defined according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III criteria[27] were enrolled. Exclusion criteria included: (1) current use of anti-inflammatory drugs including NSAIDs, oral/i.v. steroids, aspirin (> 100 mg/day), leukotriene receptor antagonists; (2) blood pressure >170/100 mm/Hg; 3) HbA1c > 7%; (3) fasting blood triglycerides > 300 mg/dL; (4) prior myocardial infarction, vascular surgery, or stroke; (5) stage II/III/IV heart failure, or liver and or renal disease; (6) pregnancy; (7) excessive alcohol use; (8) self-reported current illicit drug use; (9) intolerance or allergy any of the components present in the tested products. Every 5-7 days, all enrolled subjects were contacted by the physicians responsible for the study to report their medical condition and specific study parameters such as tolerability and dosing compliance, as well as to enable documentation of the occurrence of any side effects possibly linked to the treatment. The participating subjects were allowed to contact the physicians responsible for the study at any time. All patients provided their written informed consent to participate. All participants completed the study.

Study Procedures

The 44 participants were selected among those (N=127) who after 30 days of diet and intervention lifestyle, with adherence to therapy claimed to be > 80%, have shown a weight loss < 2% (Figure 1). They were then randomly assigned to receive for further 30 days either a daily treatment with a curcumin-based product or pure phosphatidylserine. All outcomes were measured at enrolment, at T=30 and at T = 60 days. Tolerability and side effects were collected between T=30 and T=60 -day study period. Compliance was reported at the end of the 30 days of treatment (Figure 1).

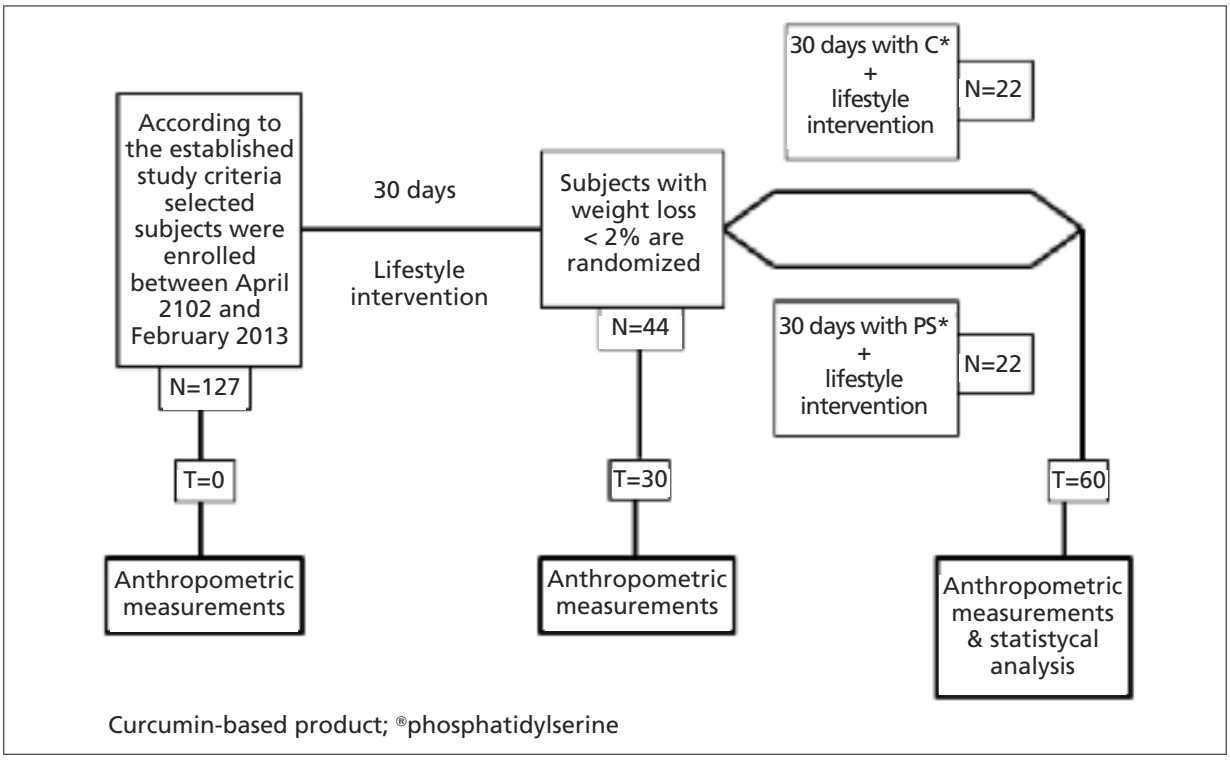

Figure 1. Scheme of the study.

Study Objectives

The principal objectives for the study were: (1) to evaluate the role of curcumin in modifying some anthropometric measurements in overweight subjects with a diagnosis of metabolic syndrome and considerable as low responder to a proper diet plus lifestyle intervention lasted 30 days; (2) to evaluate the safety and tolerability profiles of the tested products.

Lifestyle Intervention

Lifestyle interventions consisted of weekly individual sessions for nutritional education, advice reinforcement on exercise activity and peer-group psychological support. A self-monitor diary, including food consumption, daily physical activity and emotional reactions, was used as a tool for education and reinforcement. Daily caloric requirement was calculated using the Harris-Benedict equation and an individual activity factor. A diet based on a 500-kcal/day deficit from the individual estimated caloric requirement was prescribed. The diet was high in vegetables, low in salt and simple sugars, and consisted of 25% of total energy intake as protein, 20% as fat and 55% as carbohydrate. Fresh foods, at least three fish meals per week and avoiding alcohol were recommended. The prescribed physical activity program was 210 minutes per week, consisting of 70% moderate-intensity aerobic physical activity and 30% muscle-strengthening activities. Patient's dietary compliance and the average weekly level of physical activity were recorded at each session. At the end of the 30 days lifestyle intervention, participants were encouraged to continue with the same diet and physical activity program for the following month.

Treatments and Tested Products

At the end of first 30 days of lifestyle intervention, participants were randomly assigned to one out of two groups for the 30 days treatment phase. Twenty-two of them were supplemented twice a day for 1 month with a nutritional supplement formulated to be enteric-coated and containing 800 mg/dose/die of *Curcuma longa* extract (95% curcumin; Indena, Milan, Italy) complexed with sunflower phospholipids (20% phosphatidylserine) and blended with 8 mg/dose/die of piperine from *Piper nigrum* extract (Bioperine®, Sabinsa Europe GmbH, Langen, Germany). The others 22 represented the control group and were assigned to treatment with a nutritional sup-

plement containing 400 mg/dose/die of pure phosphatidylserine (Neobros®, Fidia, Abano Terme, PD, Italy). Curcumin-based dietary supplement was manufactured in SIIT (Trezzano S/N, Milan, Italy) and notified at the health authorities as Homair® (Pharmextracta, Pontenure, Piacenza, Italy). Randomization was performed using a sealed envelope system and compliance was checked by counting the left-over and returned tablets (curcumin-based product) and/or capsules (pure phosphatidylserine).

Measurements

Anthropometric measures, including body composition, were measured at enrolment and after 30 and 60 days. Body composition was measured using a body composition analyzer (Akern Bia101 Body Impedance Analizer, Pontassieve, Florence, Italy) and the software Akern Bodygram Pro 3.0. Waist and hip circumferences was measured at the level of the umbilicus and trochanter, respectively.

Statistical Analysis

To study the null hypothesis of no effect of treatments for each clinical variable we applied the two-tailed Wilcoxon test for matched pairs with signed ranks. To study the null hypothesis of no impact on clinical variables effects for each treatment we applied the two-tailed Wilcoxon Exact test. Last, to study the correlation of weight ratio, compared with baseline, and days of treatment we used a linear regression. For all the analysis statistical software used was JMP® 10 for Mac OS X (SAS Institute, Cary, NC, USA), and the threshold for statistical significance was 95%.

Results

As shown in Table I and in the first lines of Table IV where differences in terms of weight, fat (%), waistline, hip and body mass index (BMI) got at T=0 are reported) the two groups of subjects do not present any statistical difference in any parameter and are, therefore, comparable. The first 22 subjects (Table II) of the curcumin-based group after 30 days of diet and lifestyle intervention do not show any relevant change in terms of anthropometric measurement and body composition. In particular, the average weight loss is 1.88% and the BMI decrease corresponds to 2.10% with a percentage of fat reduced by 0.70% and waistline and hip circumference decreased both by about 2 cm. Differently during the second phase of treatment with a curcumin-based product all parameters, but hip circumference, decrease significantly. In particular the average weight loss is almost 5%, BMI decrease is 6.43% with fat being reduced by more than 8%. Waistline also shows a decrease of more than 4 cm. Due to the clear impact of the 30 days-treatment even the final outcomes, measured as a result of 60 days of study, result to be statistically significant. After 60 days the global weight loss is 6.70%, the BMI decrease is 8.40% with the % of fat reduced by more than 9% and more than 6 cm lost in terms of waistline. Less significant seems to be the hip circumference with globally about 3 cm lost.

As shown in Table III, the first 30 days of diet and lifestyle intervention performed on the phosphatidylserine group demonstrated results comparable with those obtained in the curcumin group. Differently, in the second 30 days, in which the phosphatidylserine treatment were added to diet and lifestyle, no significant change in any parameter was observed. The significant benefit obtained with curcumin remained evident also when the phosphatidylserine group is taken as a comparison (Table IV).

In the curcumin group, the global result calculated globally in 60 days shows the chance to lose about 1 kg every 10 days (Figure 2A); about 500 g every 10 days just because of diet and lifestyle intervention as measured during the first 30 days (Figure 2B); about 1.3 kg every 10 days just considering the second 30 days of the study where every subject was subjected to

Table I. Features of participants (N=22 per group) on enrolment.

Treatment	Curcumin-based product	Phosphatidylserine
Gender (males/females)	9/13	8/14
Age (years)	39.10 ± 16.8	41.85 ± 15.91

Values (years) are expressed as median ± standard deviation.

Table II. Anthropometric outcomes in subjects (N = 22) treated from T = 30 to T = 60 with the curcumin-based product.

Time	Weight (kg)	Fat %	Waistline (cm)	Hip (cm)	BMI
T = 0	85.2 ± 19.4	28.7 ± 6.1	101.9 ± 13.8	108.6 ± 8.2	28.6 ± 4.3
T = 30	83.6 ± 17.7	28.5 ± 5.8	99.5 ± 13.2	107.8 ± 7.9	28.0 ± 4.1
% vs. T = 0	-1.88	-0.70	-2.36	-0.74	-2.10
p vs. T = 0	0.07	0.09	0.06	0.09	0.07
T = 60	79.5 ± 18.1	26.1 ± 4.0	95.4 ± 11.8	105.1 ± 8.2	26.2 ± 4.2
% vs. T = 30	-4.91	-8.43	-4.13	- 2.51	6.43
p vs. T = 30	< 0.01	< 0.01	< 0.05	0.06	< 0.01
% vs. T = 0	-6.70	-9.06	-6.38	-3.33	-8.40
p vs. T = 0	< 0.01	< 0.01	< 0.01	< 0.05	< 0.01

BMI: Body Mass Index. Values are expressed as median ± standard deviation.

Table III. Anthropometric outcomes in subjects (N = 22) treated from T = 30 to T = 60 with phosphatidylserine.

Time	Weight (kg)	Fat %	Waistline (cm)	Hip (cm)	BMI
T = 0	86.6 ± 21.1	29.9 ± 7.5	102.5 ± 12.5	106.4 ± 7.5	29.2 ± 3.6
T = 30	85.2 ± 19.7	29.6 ± 6.3	100.2 ± 11.4	106.2 ± 7.1	29.2 ± 3.6
% vs. T = 0	-1.62	-1.01	-2.25	-0.19	0
p vs. T = 0	0.07	0.08	0.07	0.11	0.31
T = 60	83.4 ± 19.4	28.8 ± 5.6	99.5 ± 13.2	104.8 ± 7.6	28.7 ± 3.4
% vs. T = 30	-2.12	-2.71	-0.70	-1.32	-1.72
p vs. T = 30	0.06	0.06	0.07	0.06	0.06
% vs. T = 0	-3.70	-3.68	-3.93	-1.51	-1.72
p vs. T = 0	0.05	0.05	0.06	0.06	0.05

BMI: Body Mass Index. Values are expressed as median ± standard deviation.

Table IV. Treatments comparison, curcumin-based product versus phosphatidylserine, at T = 0, T = 30 and T = 60.

Time	Weight	Fat	Waistline	Hip	BMI
Δ % T = 0	-1.62	-4.2	-0.59	2.07	-1.45
p	0.07	0.05	0.07	0.06	0.08
Δ % T = 30	-1.88	-3.72	-0.70	1.50	-4.11
p	0.06	0.05	0.06	0.06	0.05
Δ % T = 60	-4.68	-9.38	-4.13	0.29	-8.71
p	< 0.05	< 0.01	< 0.05	0.06	< 0.01

BMI: Body Mass Index. Values are expressed as median ± standard deviation.

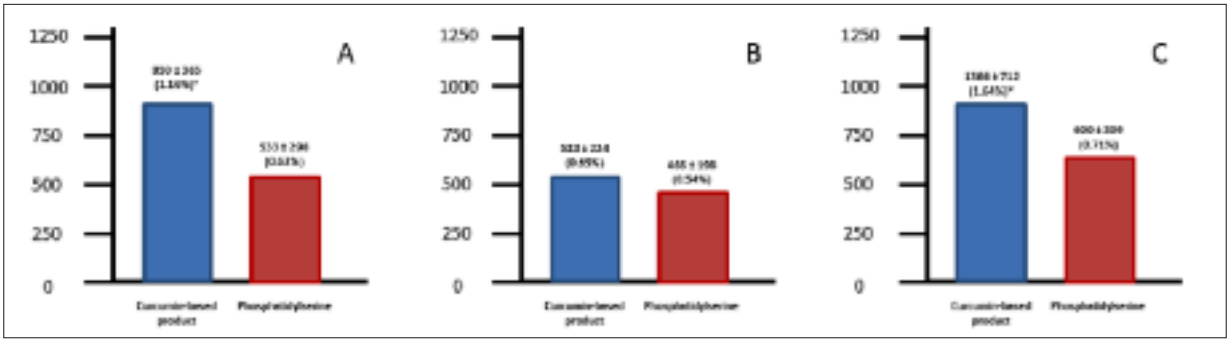

Figure 2. Linear regression of weight loss every 10 days expressed in g (and as % value) considering the global outcome after 60 days ***(A)***, the outcome of the first 30 days without treatment ***(B)*** and the outcome of the second 30 days with treatment ***(C)***. **p* < 0.05.

diet, lifestyle intervention and curcumin-based treatment (Figure 2C). No difference was observed in the phosphatidylserine group (Figure 2A, 2B and 2C).

In terms of tolerability, the two treatments appear to be similar, with only two cases of gastric burning reported by two subjects of the phosphatidylserine group likely due to the oily consistency of the active capable of creating gastric discomfort in sensitive subjects (Table V). Compliance was good in both groups. The very slight difference in favor of the phosphatidylserine group could be due to the fact that this ingredient, being oily, was formulated in soft gelatin capsules. No drop-out occurred.

Discussion

Our study was aimed at evaluating the possible role played by a bioavailable form of curcumin in further improving the effect of diet and lifestyle intervention in overweight subjects with a diagnosis of metabolic syndrome, and presenting insulin-resistance and android-type fat accumulation. Among them, we chose patients who were refractory to weight loss and with modest reduction in term of waistline and BMI, assuming that this could be due also to android-adipose tissue inflammation.

Curcumin counteracts adipose tissue inflammation and insulin-resistance[18-21]. We have decided to test a nutritional supplement product where the curcumin is complexed with phospholipids, known to enhance its poor bioavailability, and blended with piperine known to reduce its liver conjugation rate and then its urinary excretion. Curcumin complexed with phospholipids generates a phytosome containing not less than 20% of phosphatidylserine, being the remaining portion mainly phosphatidylcholine. This could be a further advantage in terms of clinical efficacy. As a matter of fact, beside the local (liver and adipose tissue) effects described for curcumin in terms of cortisol lowering properties due to the activity on 11-βHSD1[22], cortisol increases in blood circulation also due to dysregulation of Hypothalamo-Pituitary-Adrenocortical (HPA) axis. This type of cortisol increase is described to provoke stress and behavioral changes leading to appetite increase[28]. Phosphatidylserine is known to counteract systemic cortisol increase[29,30]. On these bases, we have decided to compare the effect of the curcumin-based product versus pure phosphatidylserine. Our results seem to suggest that curcumin can enhance the effects of diet and lifestyle intervention in overweight subjects affected by metabolic syndrome. In particular daily curcumin administration: (1) increased the weight loss from 1.88 to 4.91%; (2) enhanced the percentage reduction of body fat from 0.70 to 8.43%; (3) increased the waistline reduction from 2.36 to 4.14%; (4) increased the hip circumference reduction from 0.74 to 2.51% and (5) enhanced the reduction of BMI from 2.10 to 6.43%. Phosphatidylserine did not show any effect, likely due to the low dose of phosphatidylserine used. Anyway, we did not check neither the blood nor the salivary cortisol content therefore we do not know if the treatment with phosphatidylserine was able to reduce it. Actually, we assume that a positive effect of phosphatidylserine could be observed in strict relationship with a reduction, mainly by evening/night, of cortisol concentration[31]. Another aspect, possibly explaining the lack of efficacy of phosphatidylserine, could be the length of administration being 30 days of treatment a too short time.

Conclusions

This randomized, controlled study demonstrates that curcumin, as add on therapy to diet and lifestyle intervention, can be useful the get

Table V. Tolerability, compliance and side effects during 30 days of treatment with a Curcumin-based product (C) and phosphatidylserine (PS) in the enrolled subjects (N = 22 per group).

	Tolerability		Compliance		Side effects	
	C	PS	C	PS	C	PS
Very good	18	13	20	22	None	None
Good	2	4	1	0	None	None
Acceptable	2	3	1	0	None	None
Unacceptable	0	2	0	0	None	Gastric burning

better outcomes in terms of anthropometric measurements and body composition in management of overweight patient especially if this condition is characterized by parameters typical of metabolic syndrome. Our research presents some criticism which limit the strengths of our conclusion: it is not double-blinded, there was no cross-over, it lasted only 60 days, treatment phase lasted only 30 days, there was no follow-up; the number of participants was low, we did not checked chemical parameters like cortisol, sex hormones, leptin and so on. Anyway, considering our finding as preliminary, our study is one of the first demonstration that a bioavailable form of curcumin is tolerated and can affect weight management protocols and approaches. Further studies are needed to confirm in humans these data. In addition, other studies are necessary to further explore the effects of curcumin, which showed promising activity in a number of conditions[32-43].

Disclosure

Di Pierro F. is the Scientific Director of Velleja Research, the company that developed the finished product tested in this study. Debora Ranaldi is a Pharmextracta consultant. Luca Giacomelli is an Indena consultant. The others Authors do not report any conflict of interest.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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