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ScienceDirect
Nutrition Research 30 (2010) 305–313
Nutrition Research
www.nrjournal.com

Satiereal, a *Crocus sativus* L extract, reduces snacking and increases satiety in a randomized placebo-controlled study of mildly overweight, healthy women

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Received 18 January 2010; revised 14 April 2010; accepted 21 April 2010

Abstract

Snacking is an uncontrolled eating behavior, predisposing weight gain and obesity. It primarily affects the female population and is frequently associated with stress. We hypothesized that oral supplementation with Satiereal (Inoreal Ltd, Plerin, France), a novel extract of saffron stigma, may reduce snacking and enhance satiety through its suggested mood-improving effect, and thus contribute to weight loss. Healthy, mildly overweight women (N = 60) participated in this randomized, placebo-controlled, double-blind study that evaluated the efficacy of Satiereal supplementation on body weight changes over an 8-week period. Snacking frequency, the main secondary variable, was assessed by daily self-recording of episodes by the subjects in a nutrition diary. Twice a day, enrolled subjects consumed 1 capsule of Satiereal (176.5 mg extract per day (n = 31) or a matching placebo (n = 29). Caloric intake was left unrestricted during the study. At baseline, both groups were homogeneous for age, body weight, and snacking frequency. Satiereal caused a significantly greater body weight reduction than placebo after 8 weeks ($P < .01$). The mean snacking frequency was significantly decreased in the Satiereal group as compared with the placebo group ($P < .05$). Other anthropometric dimensions and vital signs remained almost unchanged in both groups. No subject withdrawal attributable to a product effect was reported throughout the trial, suggesting a good tolerability to Satiereal. Our results indicate that Satiereal consumption produces a reduction of snacking and creates a satiating effect that could contribute to body weight loss. The combination of an adequate diet with Satiereal supplementation might help subjects engaged in a weight loss program in achieving their objective.

Keywords: *Crocus sativus*; Food supplement; Placebo-controlled trial; Satiety; Snacking; Women
Abbreviations: BMI, body mass index; GI, gastrointestinal; SEM, standard error of mean.

1. Introduction

Being overweight is now acknowledged to affect more than 1 billion adults worldwide, and it is reaching epidemic proportions in the United States [1-3]. Snacking is commonly associated with an excessive intake of fat-rich foods and is considered a predisposing factor to obesity [4]. Even being mildly to moderately overweight (body mass index [BMI], 25-28 kg/m^2) increases the risk of metabolic complications such as dyslipidemia, non–insulin-dependent diabetes, circulatory disorders, hypertension, and chronic renal diseases, with all exhibiting significant morbidity [5-7].

Snacking and compulsive eating are disturbed dietary behaviors resulting from complex individual and environ-

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doi:10.1016/j.nutres.2010.04.008

mental influences, with mood disorders being an important contributor. Stress-induced eating in subjects has been paralleled with a preference for high-sugar and high-fat food consumption that is known to provide strong rewarding effects that reinforce snacking [8,9]. The incidence of such eating behaviors is significant in the general population and occurs primarily in the female population, as stress snacking affects 2% to 5% of young women [10,11].

Participating in hypocaloric weight loss programs and correcting inappropriate eating habits are often sufficient in subjects who are moderately overweight [11]. Increasing satiety, in particular through the consumption of fiber-rich foods, has been claimed to reduce body fat intake, hence contributing to a decrease in body weight [12,13]. However, for this population, maintaining adequate nutrition habits over time is difficult [14,15].

Saffron, a spice mainly used in Asia that is constituted from *Crocus sativus* L stigma and used in traditional medicine for digestive, inflammatory, and cerebral disorders, has recently raised interest [16,17]. More recently, preclinical in vivo and pilot clinical studies have reported positive anxiolytic-like and antidepressant-like effects of this herb [18-22]. Based on these investigations, we hypothesized that saffron would improve mood, hence reducing snacking and the desire to eat. Modulating abnormal frequent snacking might subsequently contribute to a better control of body weight; and by having a positive effect on stress and mood, saffron could be an adjuvant supplement for people who are involved in weight loss programs.

To test this hypothesis, the present placebo-controlled, randomized clinical trial was designed to assess the efficacy of a new food supplement containing a single patented *C sativus* stigma extract, Satiereal (Inoreal Ltd, Plerin, France), in reducing body mass and snacking in healthy women who are mildly overweight (BMI, 25-28 kg/m^2). Demonstrating the efficacy of Satiereal through improved satiety and reduced snacking could provide useful directions for the management of food intake and long-term appetite control in the currently growing obesity epidemic.

2. Methods and materials

2.1. Study design

The present study was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and tolerance of orally administered Satiereal over 8 weeks in ambulatory female volunteers who were mildly overweight. Before randomization, the protocol included a 2-week run-in period aimed at identifying "snacking" subjects using an individual nutrition survey. The daily supplementation was then initiated for 8 weeks, with reporting visits at 2-week intervals. Enrolled subjects received either active Satiereal or an indistinguishable placebo formula, taking 1 capsule for breakfast and 1 for dinner. Treatment allocation was performed using a randomized block design with a block size of 6 subjects. Allocation concealment was secured through a pharmacy-controlled randomization process using sequential treatment numbers. During the entire protocol, subjects were instructed to report all snacking events (unscheduled food consumption including solid snacks, sweets, carbohydrates, or fruits) on a daily basis in a nutrition diary. Consuming soft drink beverages was not considered as a snacking event. The routine caloric intake of subjects was left unrestricted throughout the investigation.

2.2. Subjects

Eligible subjects were healthy women, aged 25 to 45 years, who were mildly overweight and had a BMI (calculated as the weight in kilograms divided by the square of height in meters) greater than 25 kg/m^2 and less than 28 kg/m^2. They were instructed to maintain their usual nutrition regimen and lifestyle. At least 50% of the cohort was selected for the presence of compulsive snacking, although participants were not assessed specifically for their level of anxiety or stress. Exclusion criteria included history of cancer, diabetes, pathologic eating disorders (anorexia and bulimia nervosa), anxiety or depression, abnormal liver or renal function, concomitant medication with psychotropic drugs or appetite suppressants, gastric surgery, or the use of any food supplement that might interfere with the study results. This medical review was under the strict supervision of the investigator.

Written, informed consent was obtained from all women before their participation in the trial in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol, registered as EudraCT no. 2007-000524-40, was approved by the South-West and Overseas IV Ethics Committee (University Hospital, Limoges, France) and by the French Regulatory Authority (National Health Agency [*Direction Générale de la Santé*]), where the trial protocol can be accessed. All study visits and procedures were conducted at the GSR Investigation Center, Toulouse, France, from April to December 2007. The use of subjects and the study protocol were in accordance with the guidance of the CONSORT 2010 Statement that includes a checklist of necessary information for reporting parallel-group randomized trials [23].

2.3. Satiereal extract preparation

Saffron threads (red stigmas) used to prepare the Satiereal extract were mainly of Iranian origin. Stigmas were harvested from mature flowers (*C sativus* L; Iridaceae) and dried naturally. The stigma's extract was prepared according to a previously described method [18]: In brief, 120 g of dried and finely powdered stigmas was extracted with 1200 mL of 30% ethanol (10% wt/vol) using a cold percolation method. Afterward, the ethanol extract was evaporated under a vacuum at a low temperature (between 35°C and 40°C) to collect the liquid extract. This liquid extract was dried on a

microcrystalline cellulose carrier using a liquid saffron extract to cellulose ratio of 1/6 (16.7% wt/wt) to obtain the final Satiereal extract powder. Concentrations of active ingredients in the dried extract were analyzed according to validated methods and standardized using a functional test (5-HT uptake in vitro assay vs reference agent). Each colored hard gelatin capsule contained 88.25 mg of Satiereal (see Table 1 for composition). Two capsules were taken each day to provide 176.5 mg of Satiereal daily. Satiereal is notified and registered as food supplement in France by the National Trade and Fraud Authority (Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes).

2.4. Efficacy and safety assessments

At each visit, efficacy of supplementation with Satiereal compared with placebo was evaluated on body weight. The primary end point, body weight, was measured together with body composition using a calibrated impedance body fat analyzer scale (TFA100; Terraillon, Chatou, France). For each subject, body weight and the absolute differences in body weight relative to pretreatment (baseline) were assessed at 2-week intervals. Calculated differences in body weight allowed a reduced test variability and better statistical power. Assessments were performed at approximately the same time of the day to avoid daily fluctuations caused by meals.

Snacking was considered as the main secondary end point. The effects of supplementation on the frequency of snacking events were assessed at each visit. The frequency of snacking episodes was expressed as the cumulated number of episodes reported by subjects in their diary during each 2-week period. They were then stratified, depending on their snacking behavior, as "snacking" subjects (≥1 episode per day) or "nonsnacking" subjects. Waist, hip, thigh, and ankle circumferences were measured using a flexible measuring tape using standard anatomical points. Body composition, circumferences, and satiety and hunger ratings were regarded as ancillary variables. These data were only considered for analysis at baseline and at the end of the study visit.

Satiety and hunger were assessed using a specific subjective questionnaire adapted from the General Index of Food Craving [24]. The rating form included 6 questions that reflected the dimensions of hunger (1 question), satiety (1 question), and snacking (4 questions). When completing the form, individuals had to indicate on a 4-level Likert scale (1 = strongly disagree, 2 = disagree somewhat, 3 = agree somewhat, 4 = strongly agree) to what extent they agreed with each statement. The results obtained at the end of the study visit are reported as the level of approval with each statement in percentage of the maximum score for each question (100% meant that all subjects applied a rating of 4 [strongly agree]).

Table 1
Ingredient composition of capsule given to subjects

Ingredients	Placebo (mg)	Satiereal (mg)
Active ingredient (Satiereal): dried saffron (*C sativus* L) stigma extract (carrier: microcrystalline cellulose)	0.00	88.25
Microcrystalline cellulose	88.25	0.00
Nonactive ingredients: maltodextrin (bulking agent), magnesium stearate, and hydrated silica (anticaking agents)	QS	QS
Hard gelatin capsule	QS	QS

Composition for a filled gelatin capsule weighing 275 mg. QS indicates *quantum satis*.

Safety assessments included a physical examination, and clinical laboratory tests were performed on blood and urine samples at the screening visit and at the end of the study after 8 weeks of supplementation. Blood pressure and heart rate were measured after 5 minutes of rest. To determine standard glucose, total cholesterol, triglycerides, liver profile (alanine and aspartate amino transferases), creatinine, and urea, a blood sample was collected after at least 12 hours of fasting. Blood chemistry tests were performed at a local accredited clinical laboratory. Urine analysis was performed using laboratory reactive sticks (10 SG, Multistix, Bayer Diagnostics Mfg. Ltd, Bridgent, United Kingdom).

2.5. Statistical analyses

All data were expressed as means ± SEM. Statistical analyses were performed using the Stata SE v8 statistical package (Statacorp, College Station, TX, USA). A $P < .05$ was considered significant. The statistical method for comparison of primary outcomes of body weight, differences in body weight, and frequency of snacking events followed a 2-way analysis of variance mixed model (split-plot design) using interaction of group (between factor) and time (within factor) as fixed effects and subjects as a random effect. Post hoc mean comparisons of time-dependent changes from baseline in each group were performed using a Sidak test as appropriate. Between-group comparisons of changes in body weight, differences in body weight, and snacking were performed using a *t* test based on least squares mean estimates. Mean changes for secondary outcomes including body composition, body circumferences, and number of snacking events in the "snacking" subgroup were analyzed by a Student unpaired *t* test for comparisons of both arms at the end of study visit. For satiety and hunger ratings, a Student unpaired *t* test was used to compare the mean scores of responses to each statement expressed as percentage of maximum score. The estimated number of subjects necessary for this study was computed using the "sampsi" procedure in Stata. A sample size of 30 subjects in each treatment arm was established to demonstrate significant changes in body weight for an 80% power ($\beta = 0.2$) and a 2-tailed α risk of 0.05 in an unpaired comparison.

3. Results

A total of 61 subjects were enrolled in the study, with 1 subject discontinuing prematurely after 6 weeks (in the

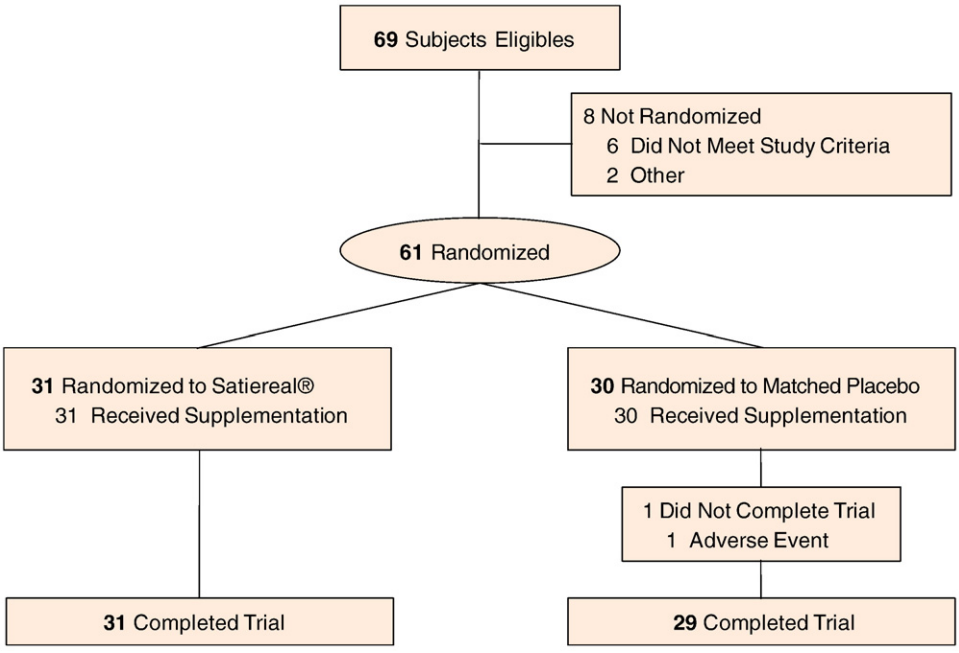

Fig. 1. Flowchart describing subject assignments for the study.

placebo group). The 60 subjects who completed the study (evaluable per protocol data set, Fig. 1) were randomly assigned to either placebo (n = 29) or Satiereal (n = 31). Table 2 lists the demographic, anthropomorphic, and clinical characteristics of enrolled subjects at the time of selection. Both study groups were identical regarding demographic data and the baseline efficacy variables. The included women had an average age of 36.1 ± 0.7 years (±SEM) and an average body weight of 73.5 ± 1.0 kg at inclusion. The average BMI was 26.8 ± 0.13 kg/m^2, consistent with the mild overweight status of enrolled subjects.

As shown in Table 2, the baseline stratification of the entire cohort relative to snacking behavior was not associated with any difference of body weight. Therefore, the impact of the snacking/nonsnacking subgroups was not considered for further body weight comparisons.

Table 2
Baseline demographic characteristics of the subjects

Parameters	Placebo (n = 29)	Satiereal (n = 31)	*P* value
Age (y)	35.9 ± 1.0	36.2 ± 1.0	.80
BMI (kg/m^2)	26.9 ± 0.2	26.7 ± 0.2	.73
Body weight (kg)	73.9 ± 1.7	73.2 ± 1.1	.72
Fat mass (%)	27.2 ± 0.8	27.6 ± 0.8	.69
Nonfat mass (%)	32.1 ± 0.6	31.4 ± 0.4	.33
Waist circumference (cm)	92.5 ± 1.7	89.7 ± 1.2	.18
Hip circumference (cm)	106.9 ± 1.5	107.2 ± 1.1	.88
Thigh circumference (cm)	58.8 ± 0.8	59.7 ± 0.8	.47
Ankle circumference (cm)	23.2 ± 0.2	22.8 ± 0.3	.28
Snacking events (n/2 wk)	12.5 ± 1.4	12.1 ± 1.6	.88
No. of "snacking" subjects	n = 16	n = 16	
Events in snacking subjects (n/2 wk)	18.1 ± 1.2	19.4 ± 1.5	.51

Values represent means ± SEM at baseline. Statistical comparisons were performed by an unpaired Student *t* test. Baseline characteristics of subjects did not show significant between-group differences by Student unpaired *t* test analysis, suggesting a uniform distribution in both arms.

3.1. Main efficacy findings

Table 3 summarizes the results obtained for body weight and snacking events during the 8-week observation period. At inclusion, body weights were similar across groups (73.9 ± 1.7 kg for placebo and 73.2 ± 1.1 kg for Satiereal). The overall model analysis for body weight did not reveal an effect of group (F = 2.47, P = .12) or time (F = 0.03, P = .99) or a significant interaction between group and time (F = 0.05, P = .99); thus, no difference in body weight in both groups at the end of study was found (73.9 ± 1.7 and 72.2 ± 1.2 kg for placebo and Satiereal, respectively). No difference was observed for between-group comparisons at each time point (*t* test, week 2 to week 8). In contrast, the analysis of body weight over time (relative to baseline) showed a significant group effect (F = 7.60, P < .001) and a trend of significance for time (F = 2.30, P = .087). Group comparisons of mean differences in body weight showed significant effects for Satiereal from week 2 onward (*t* test, P < .05 vs placebo). Satiereal supplementation resulted in a modest but statistically significant reduction of body weight after 8 weeks (−0.96 ± 0.26 kg), whereas no effect was noticed in the placebo group (−0.01 ± 1.46 kg). Fig. 2 illustrates the evolving decrease in body weight relative to baseline observed during supplementation.

The total occurrence of snacking events during the 2-week run-in period was similar in both the placebo and Satiereal groups (361 and 376 events, respectively), corresponding to a

Table 3
Change in body weight, difference in body weight, and snacking over 8 weeks of supplementation in subjects given Satiereal and placebo

Study visit	Baseline	Wk 2	Wk 4	Wk 6	Wk 8
	Body weight				
Placebo (n = 29)					
Mean (kg)	73.9 ± 1.7	74.0 ± 1.7	74.2 ± 1.7	74.2 ± 1.7	73.9 ± 1.7
P vs baseline (Sidak)		NS	NS	NS	NS
Satiereal (n = 31)					
Mean (kg)	73.2 ± 1.1	72.7 ± 1.1	72.4 ± 1.2	72.5 ± 1.1	72.2 ± 1.2
P vs baseline (Sidak)		NS	NS	NS	NS
P Satiereal vs placebo (*t* test)		NS	NS	NS	NS
	Difference in body weight				
Placebo (n = 29)					
Change (kg) relative to baseline	–	0.09 ± 0.22	0.31 ± 0.22	0.27 ± 0.25	−0.01 ± 0.26
Satiereal (n = 31)					
Change (kg) relative to baseline	–	−0.49 ± 0.16	−0.77 ± 0.21	−0.63 ± 0.25	−0.96 ± 0.26
P Satiereal vs placebo (*t* test)		*	*	*	†
	Snacking events				
Placebo (n = 29)					
Mean no. (events/2 wk)	12.5 ± 1.4	11.7 ± 1.4	9.3 ± 1.3	7.9 ± 1.4	8.9 ± 1.5
P vs baseline (Sidak)		NS	NS	‡	NS
Change (%) relative to baseline	–	0%	−22%	−42%	−28%
Satiereal (n = 31)					
Mean no. (events/2 wk)	12.1 ± 1.6	9.8 ± 1.5	7.2 ± 1.4	6.4 ± 1.2	5.8 ± 1.1
P vs baseline (Sidak)		NS	‡	§	§
P Satiereal vs placebo (*t* test)		NS	NS	NS	*
Change (%) relative to baseline	–	−17%	−38%	−49%	−55%

Values represent means ± SEM for body weight (baseline to week 8), absolute differences in body weight (week 2 to 8 relative to baseline), and number of episodes of snacking (baseline to week 8). Percentage changes for mean number of snacking events (from baseline to each time point) illustrate the observed trends in both groups during supplementation. Statistical comparisons of time-dependent changes from baseline were performed using a post hoc Sidak test as indicated (‡$P < .05$ and §$P < .01$ vs baseline). Between-group comparisons were performed using a *t* test based on least squares mean estimates (*$P < .05$ and †$P < .01$ vs placebo). *P* indicates *P* statistics; NS, not significant.

mean frequency of 12.5 ± 1.4 and 12.1 ± 1.6 snacking events per subject, respectively. Analysis of visit-related changes in snacking frequency showed a significant main effect for group (F = 10.79, $P < .001$) and for time (F = 5.58, $P < .01$), but no significant group × time interaction (F = 0.26, $P = .91$). As shown in Table 3, a significant reduction of snacking frequency relative to baseline was demonstrated with Satiereal from week 4 onward ($P < .05$, Sidak), whereas a transient significant change occurred with placebo at week 6 ($P < .05$).

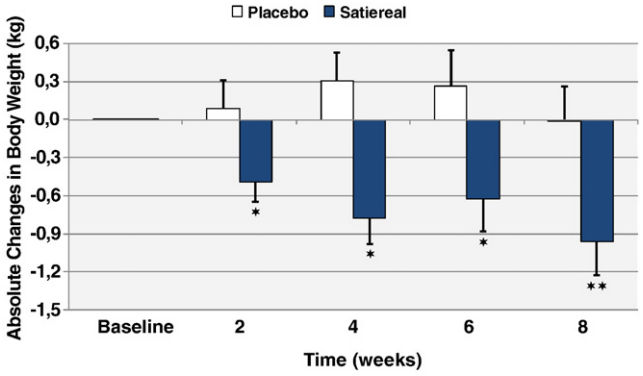

Fig. 2. Values represent means ± SEM for differences in body weight relative to baseline (week 0) in each group. A mixed-effects linear model was used for statistical analysis. Treatment groups were compared using a *t* test based on least squares mean estimates: *$P < .05$ and **$P < .01$ vs placebo. A significant difference vs placebo was found after 2 weeks of supplementation in the Satiereal group and remained throughout the study.

Table 4
Mean changes relative to baseline for secondary variables after 8 weeks of supplementation in subjects given Satiereal and placebo

Measured parameter	Placebo (n = 29)	Satiereal (n = 31)	*P* value
Body composition			
Fat mass (%)	0.07 ± 0.5	−0.01 ± 0.4	.90
Nonfat mass (%)	−0.14 ± 0.3	−0.75 ± 0.2	.12
Body circumferences			
Waist circumference (cm)	−1.12 ± 0.6	−0.69 ± 0.3	.55
Hip circumference (cm)	0.17 ± 0.3	−0.35 ± 0.3	.19
Thigh circumference (cm)	−0.41 ± 0.2	−1.08 ± 0.3	< .05
Ankle circumference (cm)	−0.57 ± 0.2	−0.44 ± 0.2	.55
Snacking events			
No. of "snacking" subjects	n = 16	n = 16	
Mean no. (events/2 wk)	−5.1 ± 9.0	−9.8 ± 5.3	< .05
Percentage change vs baseline	−23%	−51%	

Values represent means ± SEM for absolute changes relative to baseline in body composition (percentage fat and nonfat mass), circumferences (in centimeters), and snacking events (changes in mean number of events per subject at week 8 vs baseline). Percentage changes in mean snacking number between baseline and week 8 illustrate the reduction of snacking observed during supplementation. Statistical comparisons between Satiereal and placebo groups were performed using an unpaired Student *t* test. $P < .05$ indicated significant differences.

A between-group comparison of mean numbers of snacking events performed at each time point showed a significant effect of Satiereal at week 8 (t test, $P < .05$ vs placebo). From baseline to week 8 of supplementation, the number of snacking events was reduced to 5.8 ± 1.1 events per subject for Satiereal vs 8.9 ± 1.5 in the placebo group (respectively, −55% and −28% relative to baseline).

3.2. Secondary end points

The effects of supplementation on body composition, body circumferences, and snacking behavior were assessed at the last visit in comparison with baseline. Satiety and hunger ratings were assessed after 8 weeks only.

The mean changes relative to baseline for body composition and body circumferences have been summarized in Table 4. The body composition of subjects remained unchanged in both groups after 8 weeks, although a decreasing trend in relative total body water (non-fat percentage mass) was observed in the Satiereal group (31.4% ± 2.4% to 30.7% ± 2.1%, $P = .061$ vs placebo), consistent with the moderate decrease in body weight. Waist, hip, and ankle circumferences remained unchanged after 8 weeks. Thigh circumference appeared to be slightly reduced in Satiereal subjects from baseline to week 8 (−1.1 ± 0.3 cm vs −0.4 ± 0.2 cm for placebo, $P < .05$).

Snacking frequency was also assessed after stratification of the whole cohort according to snacking behavior. The frequency of snacking events for "snacking" subjects at baseline reached 19.4 ± 1.5 events per subject in the Satiereal subgroup (n = 16) and 18.1 ± 1.2 events per subject in the placebo subgroup (n = 16). After 8 weeks, Satiereal was still effective at reducing snacking relative to baseline (9.7 ± 1.5 events per subject for Satiereal, $P < .001$ and 13.0 ± 1.9 events per subject for placebo, $P < .05$). Table 4 show the absolute changes in mean number of snacking episodes at week 8 of supplementation relative to baseline, showing a stronger effect of Satiereal compared with placebo ($P < .05$).

The responses to the satiety and hunger subjective rating questionnaires were summarized in Table 5. The results showed an improvement in the Satiereal group in the "hunger" dimension (69% of subjects agreed with statement 1 vs 54% for placebo, $P < .05$) and in the "snacking" dimension (70% agreed with statement 3 vs 50% for placebo, $P < .05$). The other questions did not show significant trends indicating the apparent increased feeling of satiety in the Satiereal group.

3.3. Safety evaluation

There were no differences between the Satiereal and the placebo groups regarding tolerance and other safety assessments. The frequency of adverse events in the Satiereal group (5/31 patients, 16%) was low, and they were mild in intensity and transient in nature. Adverse events affected the digestive tract (nausea, diarrhea, and reflux). Vital signs (blood pressure and heart rate) remained unchanged in both groups at the end of the study as compared with baseline. Moreover, there were no changes in clinical biology parameters assessed at baseline and after 8 weeks of supplementation, including blood glucose, lipid levels, liver and renal enzyme functions, as well as urine laboratory checks.

Table 5
Subjective satiety and hunger ratings of subjects

Outcome question	Dim	Placebo (n = 29)	Satiereal (n = 31)	P value
		%	%	
1. Did you feel less hungry before meals?	Hu	54.0	68.8	<.05
2. Did you feel satiated more quickly during meals?	Sa	55.2	65.6	NS
3. Did the product reduce your need for snacking between meals?	Sn	50.0	69.6	<.05
4. Did the product help reduce your need for snacking related to mood?	Sn	48.5	59.4	NS
5. Did the product reduce your need for sweet snacks away from meals?	Sn	50.0	65.2	NS
6. Did the product reduce your need for fatty snacks away from meals?	Sn	57.6	68.1	NS

Values represent the mean score of approval by subjects at end of study visit (in percentage of the maximum score) for each statement. Statistical comparisons between Satiereal and placebo groups at the end of supplementation (after 8 weeks) were performed by Student unpaired t test. Dim indicates dimensions; Hu, hunger; Sa, satiety; Sn, snacking.

4. Discussion

The main results of this study indicated that daily supplementation over 8 weeks with a new food supplement containing Satiereal, a patented extract of saffron (*C sativus* L) stigma, caused a significant reduction in the frequency of snacking events and a slight but significant body weight loss as compared with placebo. These effects appeared to be associated with a subjective sensation of satiety reported by subjects receiving the active Satiereal supplementation. This is the first study, to our knowledge, describing the satiating efficacy of a saffron stigma extract used as a single ingredient in a randomized, double-blind, placebo-controlled design. The enrolled cohort included young female volunteers (25-45 years old) who were mildly overweight at selection (average BMI, 26.8 ± 0.1 kg/m^2). Approximately 50% of them had a snacking behavior defined as at least 1 snacking event per day as assessed before supplementation. All subjects were instructed not to follow any dietary constraint or program (apart from consuming the study product) and not to take any other weight loss products during the protocol. These points allowed accurate evaluation of the supplementation impact on satiety, hunger, and spontaneous snacking.

The most striking effect induced by Satiereal in this study was a progressive reduction in the frequency of snacking events illustrated by a significant 2-fold decrease in spontaneous snack food intake after 8 weeks of supplementation. The efficacy of Satiereal against snacking remained

high in the subgroup of "snacking subjects," suggesting that its action is likely to interfere to some extent with the mechanisms regulating food intake and food compulsion. The reduction of snacking by saffron was confirmed by the parallel increase of satiety sensation in subjects receiving Satiereal as measured in a satisfaction questionnaire.

The efficacy of Satiereal in reducing snacking behavior and increasing satiety was consistent with the slight, but steady and significant, decrease in body weight observed despite food being left unrestricted. A noticeable effect of placebo in reducing snacking (−28%) was observed, possibly due to the positive interaction between the physician and subjects. Nevertheless, Satiereal caused an indisputable reduction of snacking frequency over the 8-week supplementation, gradually decreasing up to 2-fold relative to baseline. This was in favor of a time-dependent setup of efficacy.

The test supplement contained a single active ingredient, Satiereal, a patented *C sativus* L stigma extract. Extracts of saffron stigma have been shown to exhibit a variety of effects including peripheral antinociceptive, anti-inflammation, antispasmodic, stomach pain relief, antioxidant, memory enhancement, and even anticancer properties, contributing to the large popularity of this spice in traditional medicine [16,17,25-30]. Higher doses have also been suggested to have anxiolytic-like and antidepressant-like potential in animal models [22,31,32].

In this trial, the proposed objective was to evaluate the potential satiating and weight-modulating action of Satiereal in healthy female volunteers who were mildly overweight. The selected study population excluded those with pathologic eating disorders like bulimia nervosa and psychiatric diseases and involved, at least in part, women who may be susceptible to snacking or to food intake increase ("snacking subjects"). Although the level of stress was not measured in participants, it was assumed that snacking could be promoted to some extent by mild anxiety or depressed mood in a number of enrolled subjects [9], eventually contributing to subsequent weight gain and being classified as overweight or obese [33].

The physiology of normal appetite and the physiopathology associated with inappropriate food intake and obesity involve complex central and peripheral mechanisms under the control of different signaling peptides in the stomach mucosa and gastrointestinal (GI) tract [34,35]. Although no experimental study has shown a direct action of saffron extract on the GI tract, the modulation of a local regulatory mechanism cannot be ruled out in explaining the potent antisnacking efficacy of Satiereal. An alternative mechanism of action to explain the Satiereal efficacy on snacking and satiety may be related to its possible impact on the central nervous system. Recent literature reports have described the potential antianxiety and antidepressant properties of saffron in vivo [21,22,31,32].

Modulation of norepinephrine and dopamine pathways, as well as selective serotonin reuptake inhibition, represent likely targets for a central component of saffron efficacy. Recent clinical data have also suggested an impact on mild-to-moderate depression. Although these studies were performed using either saffron petal or stigma extracts on small cohorts of patients and did not evaluate dose dependency, substantial improvements of symptoms were reported, with an antidepressant efficacy similar to that observed with synthetic drugs used as positive comparators [19,36-38]. A global health survey performed during the course of the present study, at the end of supplementation, and also several weeks later (data not shown) demonstrated that subjects in the Satiereal group felt significantly more alert and energetic than those in the placebo group. This was consistent with a possible role of Satiereal to improve mental and emotional well-being.

Weight management using dietary herbal supplements is subject to debate due to the diverse nature of ingredients found in a number of formulas. Protocols using a combination of dietary supplements and a hypocaloric diet program make it difficult to assess the contribution of each component. Moreover, safety and tolerance issues may occur, particularly because a proportion of these supplement formulas contains natural sympathomimetic stimulants including *Ephedra*, caffeine, or bitter orange. Those that use these products generally report 2- to 3-fold higher rates of adverse events, such as GI, autonomic, or even cardiac events [39]. Interestingly, a recent clinical and laboratory safety evaluation of saffron stigma tablets, testing up to 400 mg daily over 7 days in healthy volunteers, demonstrated minor changes in hematology and biochemistry parameters. However, these alterations remained in the reference ranges and were not clinically significant [40]. Consistent with these results, supplementation with Satiereal in the present study was associated with extremely good tolerance, predicting safe usage over several months.

The present study has several limitations. The primary end point of the trial, body weight change, is only marginally reduced by the intervention (1 kg loss over 8 weeks in the active arm) and is only in mildly overweight subjects (BMI, 25-28 kg/m^2). As a result, it is not possible to predict a potential body weight–reducing effect in subjects who are more severely overweight (>28 kg/m^2). However, it was considered that enrollment of mildly to moderately overweight subjects in this trial allowed excluding typical obese subjects who present generally a multifactorial etiology or pathologic endocrine process. Another limitation of the study is the lack of stress/anxiety assessment at selection. Although a certain level of stress and anxiety was anticipated in a part of the cohort, for the subgroup of "snacking subjects" in particular, this parameter was not quantified. The objective of the study was not to focus on symptoms of stress and anxiety in subjects but instead to evaluate the potential benefit of Satiereal on snacking and satiety that could lead to improved mood.

This study only evaluated one dose of Satiereal. The assessment of a possible dose-efficacy relationship would

have been instrumental in demonstrating its satiating action, but such an approach would have taken much longer because an appropriate trial requires a crossover design. However, the daily dose of Satiereal taken by subjects in the trial was chosen according to the vast majority of literature reports exhibiting a positive effect of saffron on mood.

Lastly, despite the present new data and the current knowledge about saffron's properties, the mechanisms suggested to contribute to reducing snacking remain speculative, awaiting elucidation of the central and/or peripheral targets involved in its neuropharmacology.

In conclusion, the present results support the working hypothesis that Satiereal, a new patented stigma extract of *C sativus* L, may produce a certain level of satiation susceptible to impact snacking behavior. A possible consequence may be that Satiereal could contribute, although to a limited extent, to body weight reduction. One may speculate that Satiereal could be a useful adjunct supplementation for people engaged in a weight loss program, in particular for women who appear to be the most affected. Further experiments are necessary to assess the potential benefit of using Satiereal to sustain the commitment of subjects trying to control their weight.

Acknowledgment

This research was funded by Inoreal, Ltd (Plerin, France), the supplier of Satiereal extract. Inoreal Ltd did not contribute to the reporting of the results or the preparation of the manuscript.

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