NATURAL BIOACTIVE COMPOUNDS GROUP
INSTITUTO DE BIOLOGIA MOLECULAR Y CELULAR
UNIVERSIDAD MIGUEL HERNÁNDEZ DE ELCHE

Hibiscus and lemon verbena polyphenols: Assessment for weight management in overweight volunteers. Appetite control and satiety.

FINAL REPORT

Introduction

Emerging scientific evidence indicates that supplementation with dietary supplements may be an alternative in the treatment of obesity and other metabolic disorders. Recent *in vitro* studies suggest that *Lippia citriodora* (LC) and *Hibiscus sabdariffa* (HS) polyphenolic extracts have favorable effects on reducing the accumulation of intracellular lipids and to decrease high glucose-induced oxidative stress and inflammation in adipose tissue through the regulation of different metabolic pathways (Fernández-Arroyo et al., 2011; Herranz-Lopez et al., 2015; Herranz-Lopez et al., 2012; Joven et al., 2012; Joven et al., 2014).

Most of these effects have been corroborated in animal hyperlipidemic models in which the continuous consumption of polyphenols from these extracts prevented fatty liver disease (FLD) and improved lipid metabolism.

A previous study showed that the consumption of MetabolAid® (*Lippia citriodora* extract + *Hibiscus sabdariffa* extract) for two months in overweight women decreased weight, improved anthropometric parameters, decreased systolic blood pressure and heart beat and improved blood lipid profile. Although appetite assessment was not strictly evaluated, monitoring of the volunteers throughout the study indicated that most individuals of the MetabolAid® group experienced a satiating effect.

Study Objectives

Due to the potential satiating effect of the food supplement MetabolAid® on appetite indicated by the volunteers in the previous report, the objective of this study was to examine some aspects related to appetite, hunger and satiety using a visual scale. In addition to confirming the effect on body weight as well as on several metabolic and hematological parameters associated with metabolic syndrome on overweight volunteers.

Methods

Study population

Participants for the study were recruited from the city of Elche, Alicante, Spain. Forty-seven healthy women, aged 30-75 years old, with a body mass index (BMI) from 24 to 35 kg/m^2 were recruited into the study. During enrollment period in dietetics, 70 prospective volunteers responded to recruitment. Fifty-four passed a telephone-based health screening and interview as well as the anthropometrical evaluation (Figure 1). Exclusion criteria included presence of any obesity-related pathology, use of prescription medication for cholesterol or hypertension, consumption of antioxidant supplements/drugs, alcohol addicts and women who were pregnant or lactating. After recruitment, the subjects were randomly assigned into the placebo or experimental group.

Prior to participate in the study, subjects were informed by the investigators about the product and the study procedures. Informed consent form (ICF) was obtained before the subject entered the study. Based on the above criteria, 54 consenting volunteers were selected to participate in the study. Seven subjects dropped out during the study and forty-seven subjects completed the study. There were various reasons to excluded participants including personal conflict, loss of dietary guidelines and lost to follow-up (Figure 1). All subjects provided written ICF and the Ethical Committee of the Miguel Hernández University of Elche approved the study protocol (reference IB.ER.01.15). The study was conducted in accord with the Helsinki Declaration (1983 version).

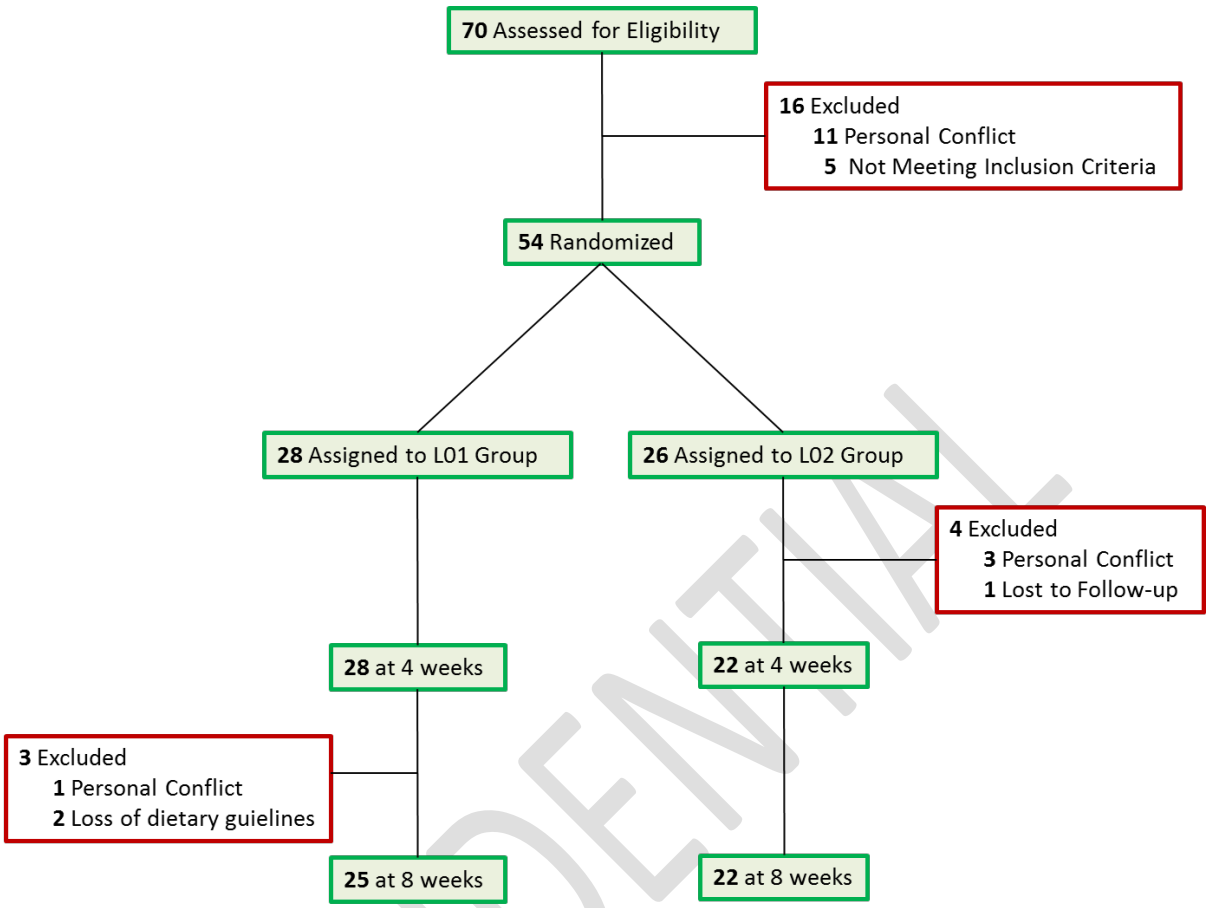

Figure 1. Study design and flow chart of the triple blind, placebo controlled and randomized trial for satiety using MetabolAid® on overweight volunteers

Study design

The study was a triple blind, placebo controlled and randomized trial. The treatment group (L1) (mean age 51) received one capsule containing 500 mg MetabolAid® (*Lippia citriodora* extract + *Hibiscus sabdariffa* extract), 150 mg excipients (magnesium stearate) and coating (gelatin). The control group (L2) (mean age 51) received one capsule of placebo (400 mg of crystalline microcellulose). Volunteers were instructed to take one Metabolaid® capsule or one placebo capsules 20-30 minutes prior to breakfast every day during two months. Compliance of the subjects with the ingestion of capsules and diet was assessed at each clinic visit or by telephone interviews every week. Women were instructed by a qualified dietician to follow an isocaloric diet with a normal hydration and to walk for at least 30 minutes per day. The study duration was 2 months.

Efficacy outcomes.

The efficacy outcome measurements were taken at baseline, and at different times of the intervention period. Moreover, during each visit symptoms or side effects were recorded. The following parameters were assessed:

Anthropometric measurements were taken at baseline, 30 and 60 days of the intervention period. Anthropometric measurements included body weight, height, triceps, abdomen and biceps skinfold thickness besides arm, waist and hip circumference. Body weight and height were measured using a scale with height measuring rod. Body mass index (BMI) was derived from body weight and height by the equation BMI = Body weight (Kg) / height^2 (m). Skinfolds thicknesses were measured using a skinfold caliper and waist and hip circumference were measured using a tape measure. Percentage of body fat (% BF) was derived from waist (Pabd1) and hip (Pabd2) circumference by a Weltman equation.

Vital signs (Systolic and diastolic blood pressure and heart beat) were also measured at rest at the beginning, 30 and 60 days of the intervention using an Ecomed blood pressure monitor.

Appetite sensations were assayed using the visual analogue scale (VAS) technique, a subjective Appetite Rating, at fasting at the 15, 30, 45 and 60 days of the intervention. The VAS allow to assess the physiological and psychological dimensions of appetite sensations, hunger, satiety, fullness, prospective food consumption, desire to eat something fatty, salty, sweet or savoury, and palatability of the meals. Operationally a VAS is a horizontal line anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state.

Eight appetite sensations were measured: desire to eat (“How strong is your desire to eat?”; “Very low desire” to “Very high desire”), hunger (“How hungry do you feel?”; “Not at all hungry” to “Extremely hungry”), fullness (“How full do you feel?”; “Not at all full” to “Extremely full”), prospective food consumption (PFC) (“How much food do you think you could eat?”; “None at all” to “A large amount”) and desire to eat something fatty, salty, sweet or savoury (“Would you like to eat something…?”, “Yes, very much” to “No, not at all”).

Quality of life was assessed at the beginning and end of supplementation using the FS-36^{-v2} questionnaire for general health. The SF-36 Health Questionnaire is one of the most used and evaluated Health Quality of Life instruments and is a suitable instrument for use in medical research and clinical practice, because the SF-36 showed good discrimination between patient groups.

Health Survey asks 36 questions to measure functional health and well-being from the patient's point of view. Patients completed the SF-36 questionnaire when they were selected and at the end of the study, after two months.

The 36 items of the instrument cover the following scales: general health, physical function, physical role, body pain, vitality, social function, emotional role and mental health.

The SF-36 questionnaire consisting of 36 items clustered to measure eight: Physical Functioning (PF), Role Limitations due to Physical Health (Role-Physical, RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (Role-Emotional, RE) and Mental Health (MH). There is in addition a single-item measure of Health Transition (HT). The scales of the SF-36 are ordered so that the highest score corresponds to fewer limitations or better health state.

Statistical Analysis

The results were calculated as the mean of the only participants who completed the study, regardless of whether they dropped out. Statistical analyses were performed by Student's unpaired t-test using Graphpad Prism software. Outcome variables were assessed for conformance to the normal distribution and transformed if necessary. Data were reported as mean ± SD. Reported *p* -values were two-sided and a P-value of 0.05 or less was considered statistically significant for between-group comparisons. All comparisons reported in this study are established between the placebo and the MetabolAid® groups. *p <0.05; ** p <0.01, *** p <0.001; **** p <0.0001.

Results

Anthropometric measurements

Baseline characteristics of the two groups were well matched and no significant differences were found at baseline. The results showed an overall improvement of all anthropometric

parameters in the group having MetabolAid® compared to placebo after two months, particularly in the body weight, triceps skinfold thickness, body fat and hip circumference (Table 2).

MetabolAid® group exhibited a higher decrease of body weight compared to the control group and significant differences were observed between the placebo and experimental intervention groups only after one month (-1.44 ± 0.27 kg vs. -2.46 ± 0.28 kg, respectively, $p < 0.05$) being higher after two months of product consumption (-2.08 ± 0.3 kg vs. -3.48 ± 0.4 kg, respectively, $p < 0.05$).

Furthermore, MetabolAid® group exhibited a statistical significant higher decrease in all skinfold thicknesses measured (triceps, biceps and abdominal) compared to the control group. This reduction was remarkable in the triceps skinfold thickness (-0.15 ± 0.15 cm vs. -1.64 ± 0.29 cm, respectively, $p< 0.001$). All perimeters were also reduced over the two months treatment. The hip circumference decreased over time in both groups but the experimental group lost significantly more hip circumference (-3.50 ± 0.37 cm) compared to the placebo group (-1.30 ± 0.28 cm, $p < 0.0001$) after two months of product use (table 2)

Consistently with this data, the abdominal circumference at umbilicus level (Pabd2) was reduced by 2.57 ± 0.34 cm in the group having MetabolAid, whereas this parameter only decreased 0.80 ± 0.55 cm in the placebo group, $p < 0.01$. The arm circumference also exhibited a significant decrease compared to the placebo group (-0.22 ± 0.23 cm vs. -0.32 ± 0.08 kg, respectively, $p < 0.01$) (table 2). The body fat (BF) decreased over time in both groups but the experimental group lost significantly more body fat (1.50 ± 0.14 %) compared to the placebo group (0.75 ± 0.13 %) (table 2).

Heart rate and blood pressure

On the other hand, a significant decrease was observed in the heart rate of the patients of the group consuming MetabolAid® after 60 days (74 to 69 beats per minute) (table 1). After two months, the group having MetabolAid® exhibited a significant reduction of both the systolic blood pressure (placebo: 0.70 ± 0.30 bpm vs. MetabolAid®: -3.50 ± 0.61 bpm, $p < 0.0001$) and diastolic blood pressure (placebo: 0 ± 0.50 bpm vs. MetabolAid®: -3.92 ± 0.63 bpm, $p < 0.0001$) (table 2).

Appetite sensations

In the Visual Analogue Scales analyzed statistically significant differences were seen with regards to feelings of appetite, hunger and satiation in the group having MetabolAid compared to placebo after 1 month, being these differences greeter after 45 days and 2 months of product consumption (Figure 2 and table 3).

MetabolAid® consumption significantly decreased the feeling of hunger consistently throughout the two months of the treatment. The mean of feeling of hunger decreased from 5.92 (day 15) to 2.58 (day 60) in the MetabolAid group whereas an increase from 6.18 (day 15) to 6.41 (day 60) was observed for the placebo group (Fig. 2).

Satiety level showed an increase from 5.04 (day 15) to 7.58 (day 60) in the MetabolAid® group, whereas this parameter decreased from 4.82 (day 15) to 4.22 (day 60) in the placebo group. An increase was also observed in the response to the question “How full do you feel?” in the MetabolAid® group (from 4.65 to 7.46) compared to the placebo group that exhibited a weak decrease (from 4.45 to 3.52) (Fig. 2).

After two months of intervention a much lower score was also confirmed in the response to the question "How much do you think you can eat?" in the MetabolAid group (from 5.57 to 2.54) compared to the placebo group (7.22 to 7.33). Finally, women in the control group showed greater appetite for sweet and salty foods compared to the women consuming MetabolAid® (Fig. 2).

SF-36 Health Questionnaire

After two months of intervention, the SF-36 questionnaire was evaluated. The Metabolaid group was confirmed a marked improvement in their quality of life (Figure 3 A and B). The group having MetabolAid improved the scores in all the dimensions analyzed. However, the placebo group did not show any significant improvement in any of the items analyzed (Figure 3 C and D).

Adverse events

Treatment of overweight and obese subjects with MetabolAid® was well-tolerated. No subjects had adverse side effects during intervention period.

Conclusions

1. The consumption of 500 mg per day of MetabolAid® together with an isocaloric diet for two months resulted in a higher reductions of body weight, body fat, triceps, biceps and abdominal skinfold thicknesses and arm, hip and waist circumference compared to the group having a placebo together with the same isocaloric diet

2. The consumption of MetabolAid® also significantly decreased systolic blood pressure (-3.50 mm Hg, $p < 0.0001$), diastolic blood pressure (-3.92 mm Hg, $p < 0.0001$) and heart rate (-4.68, $p < 0.0001$) compared to the placebo group, confirming the results of the previous intervention study.

3. The consumption of 500 mg per day of MetabolAid produced a decrease in hunger and appetite for tasty, fatty, sweet and salty foods and also increased the feeling of satiety and fullness. Women having MetabolAid showed improvement towards eating food anxiously.

4. In conclusion, the results show that the consumption of MetabolAid® for two months in overweight women decreased weight, improved anthropometric parameters, decreased systolic, diastolic blood pressure and heart rate, and increased satiety and fullness, decreasing hunger and prospective food consumption. Therefore, the consumption of 500 mg/day of MetabolAid®, in combination to isocaloric diet, may be considered as a dietary supplement for weight management and the prevention of metabolic syndrome.

5. Moreover, the MetabolAid® group showed an improvement in General health, Mental health, Body pain and Vitality.

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Table 1. Anthropometric measurements and Vital signs after one and two months. Intra-group statistical analysis at endpoint compared to the baseline. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ (Mean ± SD).

	Placebo (L2; N= 22)			MetabolAid® (L1; N= 25)		
Anthropometric parameters	**BASELINE**	**MONTH 1**	**MONTH 2**	**BASELINE**	**MONTH 1**	**MONTH 2**
Body weight	75.64 ± 12.92	74.20 ± 12.62****	73.56 ± 12.57****	75.26 ± 9.06	72.80± 9.45****	71.78 ± 9.06****
Body mass index (BMI)	29.78 ± 4.19	29.15 ± 4.08****	28.95 ± 4.01****	29.60 ± 3.40	28.60 ± 3.52****	28.26 ± 3.46****
Arm circumference (cm)	31.20 ± 3.80	31.23 ± 3.80	30.98 ± 4.10	30.58 ± 1.67	30.47 ± 1.83	30.26 ± 1.76****
Pabd 1 (cm)	94.02 ± 13.03	92.84 ± 12.86***	92.05 ± 13.16****	90.96 ± 9.03	88.96 ± 9.18****	88.01 ± 8.90****
Pabd 2 (cm)	100.7 ± 14.01	100.5 ± 14.21	99.90 ± 14.54**	96.42 ± 7.93	94.84 ± 7.87****	93.85 ± 7.95****
Hip circumference (cm)	108.8 ± 8.73	108.15 ± 8.55**	107.5 ± 8.48***	110.4 ± 7.23	108.2 ± 7.56****	106.9 ± 7.48****
Triceps skinfold thickness	43.25 ± 9.28	43.15 ± 9.34	43.10 ± 9.42	41.62 ± 8.18	40.96 ± 8-08**	39.98 ± 7.97****
Biceps skinfold thickness (mm)	41.53±14.46	41.25±14.35*	41.09±14.35*	38.33±10.63	37.61±10.87*	36.87±10.52****
Abdominal skinfold thickness (mm)	35.72±11.15	35.39±10.68	34.39±10.68	41.45±12.89	39.72±12.95***	38.60±13.08***
% Body fat (BF)	67.39 ± 5.19	66.95 ± 5.11**	66.64 ± 5.15****	66.65 ± 3.59	65.66 ± 3.70****	65.15 ± 3.64****
Vital signs						
Hear rate (BPM)	71.41 ± 8.89	71.95 ± 8.85	72.09 ± 9.24	73.32 ± 9.70	70.84 ± 7.54*	68.64 ± 7.07****
Systolic BP mm Hg	114.5 ± 23.26	115.1 ± 23.55*	115.2 ± 23.13*	117.4 ± 12.13	115.1 ± 12.82**	113.9 ± 12.5****
Diastolic BP mm Hg	73.73 ± 10.57	74.05 ± 11.50	73.73 ± 10.70	73.40 ± 5.00	71.28 ± 5.89****	69.48 ± 6.62****

PAbd1: Abdominal circumference anteriorly midway between the xiphoid process of sternum and the umbilicus and laterally between the lower end of the rib cage and iliac crests. PAbd2: Abdominal circumference at umbilicus level (Waist circumference).

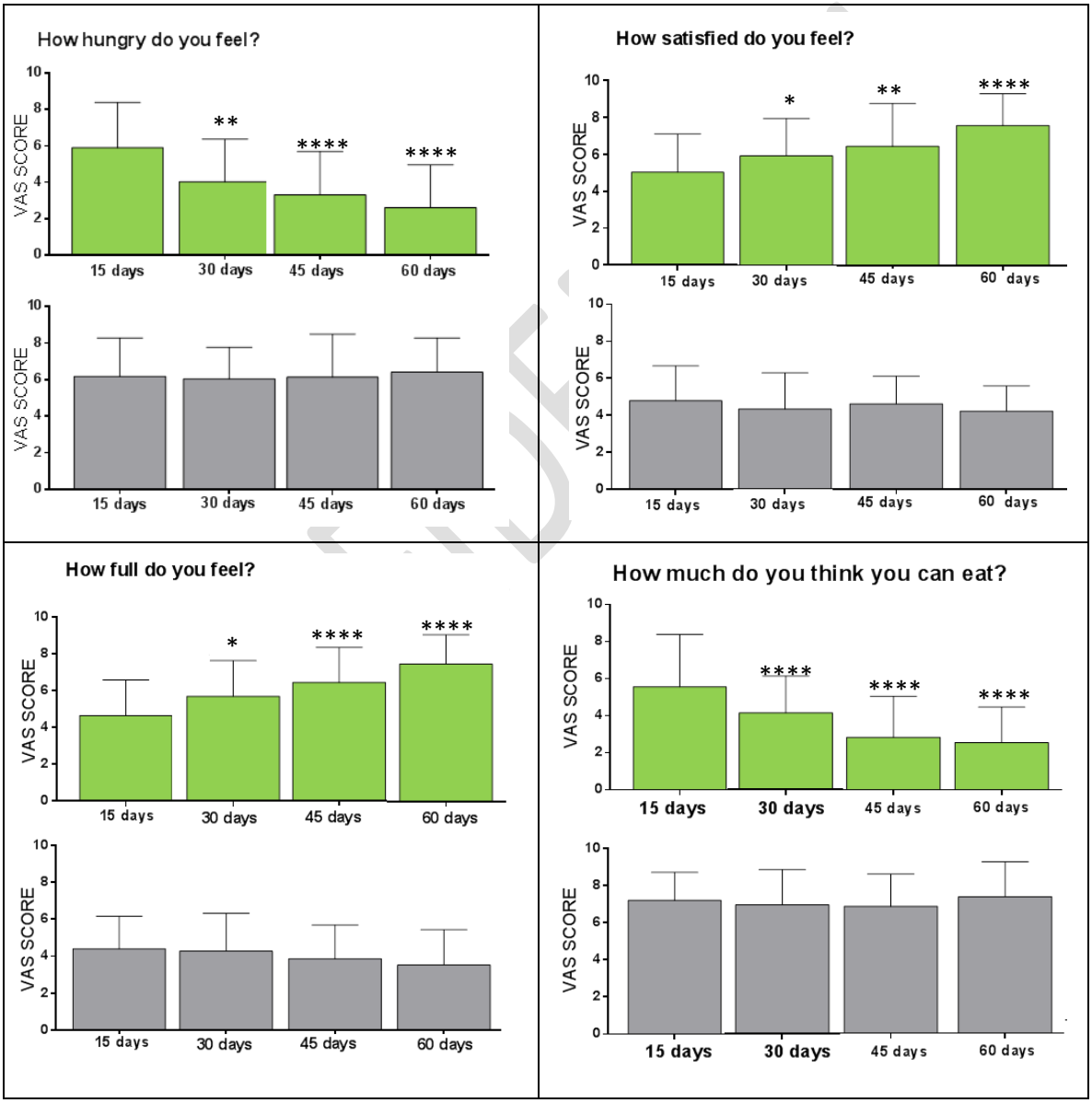
Table 2. Changes in body weight, body mass index, systolic and diastolic pressure, heart rate, triceps skinfold, biceps skinfold, abdomen skinfold, arm circumference, waist circumference, hip circumference, body fat measurements after one and two months. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ compared with Placebo. Data represent change after one month and two months (Mean ± Std. Error).

	Changes in the first month		Changes in two months	
Anthropometric parameters	**Placebo (L2; N= 22)**	**MetabolAid® (L1; N= 25)**	**Placebo (L2; N= 22)**	**MetabolAid® (L1; N= 25)**
Body weight (Kg)	-1.44 ± 0.27	-2.46 ± 0.28*	-2.08 ± 0.30	-3.48 ± 0.40*
Body mass index (BMI)	-0.63 ± 0.14	-1.00 ± 0.15*	-0,83 ± 0.12	-1,37 ± 0,16*
Arm circumference (cm)	0.03±0.03	-0.11±0.06	-0.22 ± 0.23	-0.32 ± 0.08**
Pabd1	1.18±0.29	-2.00±0.27*	-1.97 ± 0.37	-2.95 ± 0.36
Pabd2	0.20±0.54	-1.58±0.25**	-0.80 ± 0.55	-2.57 ± 0.34**
Hip circumference (cm)	0.65±0.23	-2.20±0.32***	-1.30 ± 0.28	-3.50 ± 0.37****
Triceps skinfold thickness (mm)	-0.10 ± 0.16	-0.66±0.18*	-0.15 ± 0.15	-1.64 ± 0.29****
Biceps skinfold thickness (mm)	-0.28±0.14	-0.62±0.22	-0.44 ± 0.19	-1.46 ± 0.29**
Abdominal skinfold thickness (mm)	-0.33±0.36	-1.73±0.37*	-1.33 ± 0.29	-2.84 ± 0.53*
% Body fat (BF)	0.44±0.12	-0.99±0.11**	-0.75 ± 0.13	-1.50 ± 0.14***
Vital signs				
Heart rate (BPM)	0.54 ± 0.28	-2.48 ± 0.89****	0.68 ± 0.36	-4.68 ± 0.36****
Systolic BP mm Hg	0.60 ± 0.28	-2.30 ± 0.64****	0.70 ± 0.30	-3.50 ± 0.61****
Diastolic BP mm Hg	0.32 ± 0.43	-2.12 ± 0.39****	0 ± 0.50	-3.92 ± 0.63****

PAbd1: Abdominal circumference anteriorly midway between the xiphoid process of sternum and the umbilicus and laterally between the lower end of the rib cage and iliac crests. PAbd2: Abdominal circumference at umbilicus level (Waist circumference).

Figure 2. Subjective scores for hunger, satiety, fullness and prospective food consumption in the MetabolAid® group (L1: n=25: Green bars) and the control group (L2: n=22: Grey bars) on four test days (test 1: day 15; test 2: day 30; test 3: day 45; test 4: day 60). Values are mean. VAS SCORE:

*How hungry do you feel? Score 0 "I am not hungry at all" and score 10 "I have never been hungrier"
*How satisfied do you feel? Score 0 "I am completely empty" and score 10 "I cannot eat another bite".
*How full do you feel? Score 0 "Not at all full" and score 10 "Totally full".
*How much do you think you can eat? Score 0 "Nothing at all" and score 10 "A lot".
*Would you like to eat something sweet? / Would you like to eat something salty? / Would you like to eat something savoury? / Would you like to eat something fatty? Score 0 "Yes, very much" and score 10 "No, not at all"



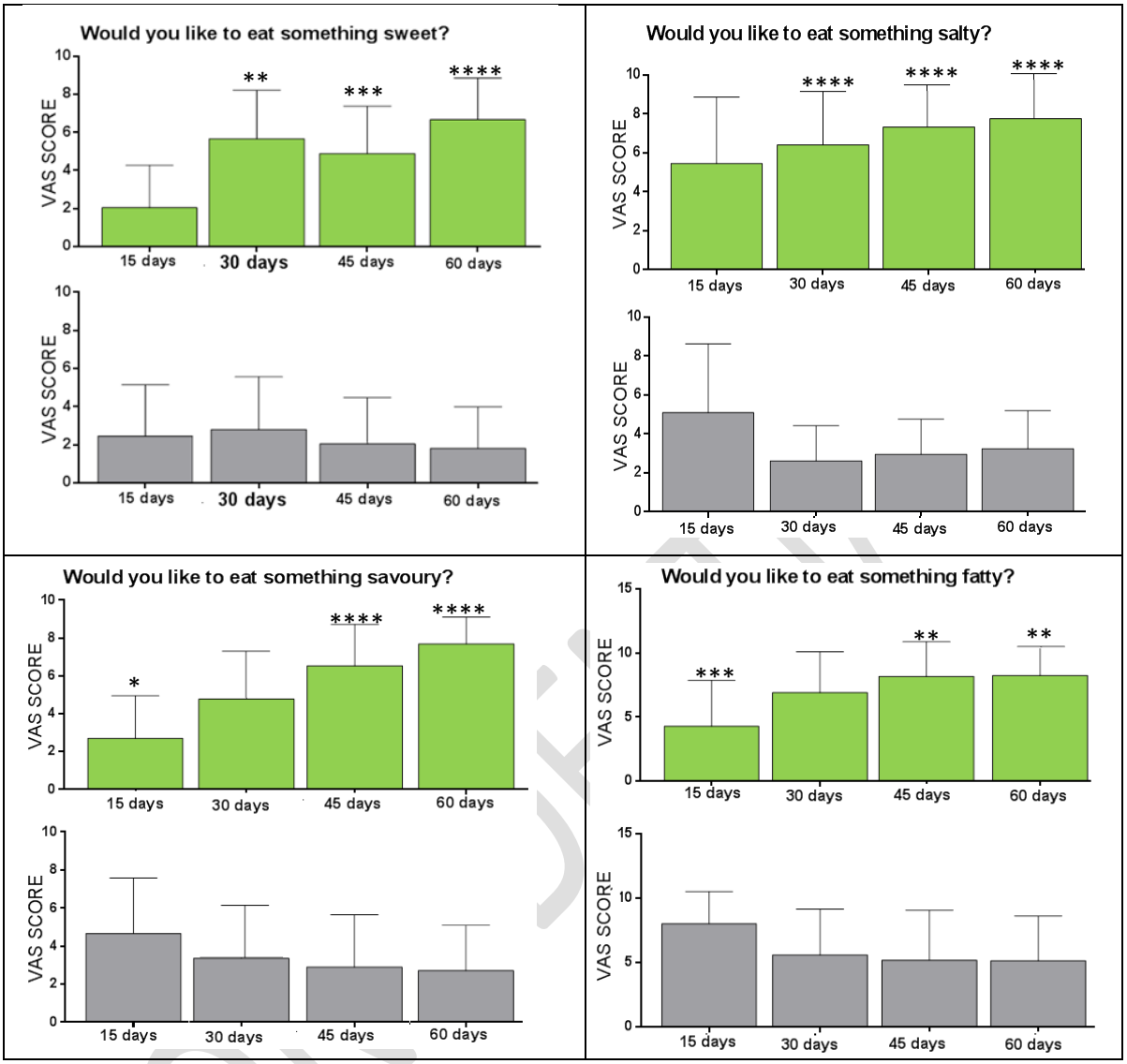
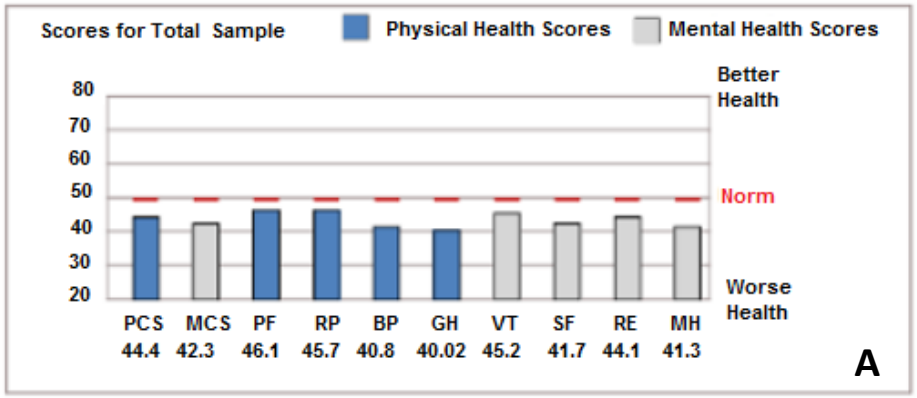
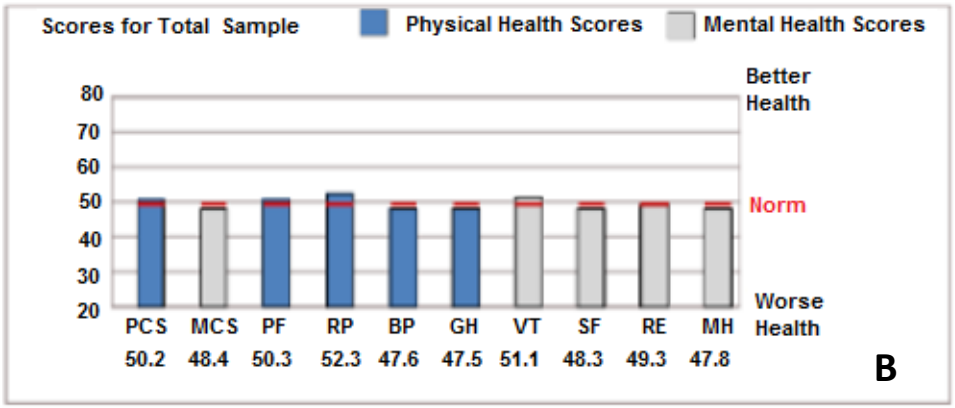


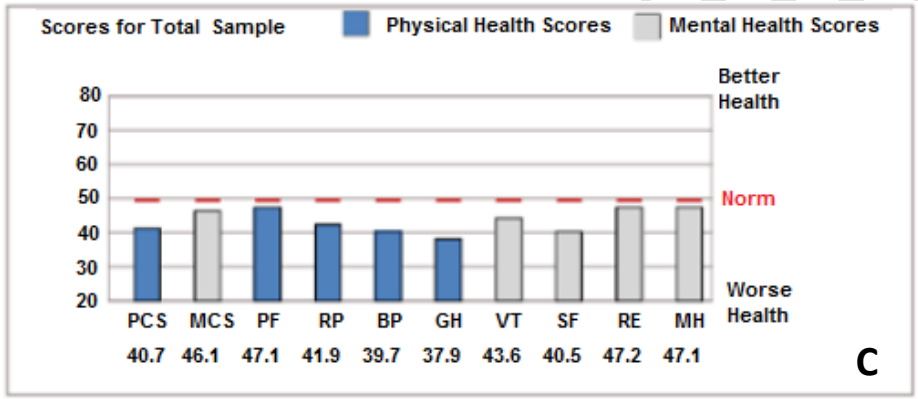
Table 3. VAS Changes of hunger sensations in the MetabolAid® group (n=25) and the control group (n=22) on four test days. Data represent responses of each evaluation after 15 days. * p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001 compared with Placebo. (Mean ± Sd).

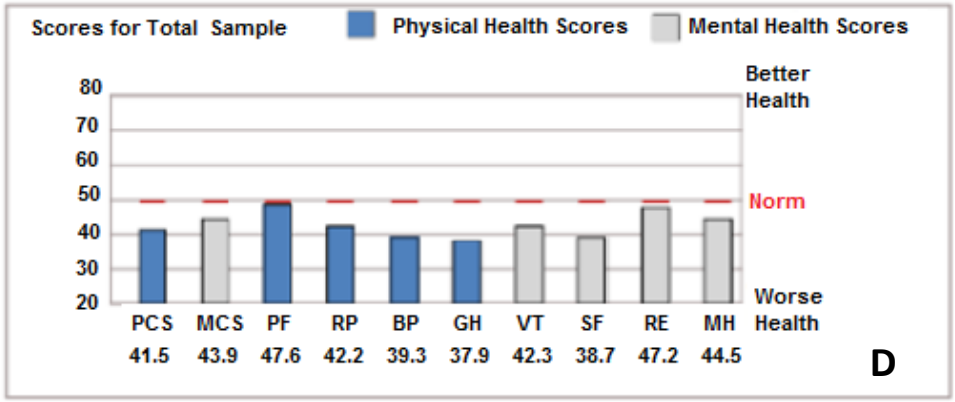
Scale items	15 days		30 days		45 days		60 days	
	MetabolAid	Placebo	MetabolAid	Placebo	MetabolAid	Placebo	MetabolAid	Placebo
How hungry do you feel?	5.92±2.48	6.18±2.36	4.00±2.34**	6.05±1.73	3.29±2.37****	6.18±2.11	2.58±2.35****	6.41±1.87
How satisfied do you feel?	5.04±2.07	4.82±1.89	5.92±2.02*	4.32±1.95	6.45±2.32**	4.63±1.50	7.58±1.72****	4.22±1.38
How full do you feel?	4.65±1.94	4.45±1.76	5.76±1.80*	4.30±1.90	6.42±1.87****	3.86±1.83	7.46±1.59****	3.52±1.91
How much do you think you can eat?	5.57±2.83	7.22±1.52	4.14±1.98****	6.95±1.90	2.83±2.20****	6.82±1.74	2.54±1.90****	7.33±1.90
Would you like to eat something sweet?	2.04±2.23	2.45±2.70	5.65±2.55**	2.80±2.76	4.83±2.73***	1.95±2.13	6.67±2.18****	1.82±2.17
Would you like to eat something salty?	5.45±3.42	5.09±3.53	6.38±2.73****	2.60±1.79	7.57±2.27****	2.86±2.59	7.75±2.19****	3.09±2.72
Would you like to eat something savoury?	2.70±2.25*	4.68±2.93	4.96±2.51	3.68±2.73	6.50±2.19****	2.90±2.75	7.67±1.40****	2.71±2.47
Would you like to eat something fatty?	4.29±3.58***	8.07±2.52	6.87±3.18	5.60±3.58	8.13±2.71**	5.18±3.88	8.21±2.47**	5.14±3.48

Figure 3. Norm-based SF-36 results Graphs representing the Normalized score of the SF-36 questionnaire in the Placebo (C and D) and MetabolAid (A and B) group at the beginning (A and C) and at the end of the study (B and C). Abbreviations: Physical Component Summary (PCS); Mental Component Summary (MCS); physical functioning (PF); role physical (RP); bodily pain (BP); general health (GH); vitality (VT); social functioning (SF); role emotional (RE); mental health (MH); norm-based score (NBS).









Elche, 12 April 2017

Vicente Micol Molina, PhD
Professor of Biochemistry and Molecular Biology
Institute of Molecular and Cell Biology
Miguel Hernández University