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# Capsaicinoids Increase Resting Metabolic Rate in Healthy Individuals under Fasting Condition

**Morde A, Rai D, Acharya M and Padigaru M***

OmniActive Health Technologies, Phoenix House, Senapati Bapat Marg, Lower Parel, Mumbai, India

***Corresponding author:** Padigaru M, OmniActive Health Technologies, Phoenix House, T- 8, A Wing 462 Senapati Bapat Marg, Lower Parel, Mumbai 400 013, India, Tel: +91 98866 99941, E-mail: m.padigaru@omniactives.com

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## Abstract

Obesity is a chronic metabolic condition of energy imbalance where energy intake exceeds energy expenditure. Resting energy expenditure (REE) represents calories burned at rest and accounts for >60% of total energy expenditure and is an important target for management of obesity. Capsaicinoids, extracted from *Capsicum annuum* have previously been shown to increase metabolism, lipolysis & induce satiety.

We conducted a randomized, double-blind, placebo-controlled, cross-over study to evaluate the change in REE in response to a uniquely formulated capsaicinoid extract (CAP) using indirect calorimetry under fasting state. In addition, oxygen consumption (VO2) and carbon dioxide production (VCO2) rates, as well as subject's innate thermal sensation using American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) scale were measured at baseline, 1, 2, 3 & 4 hours post supplementation. Safety assessments included measurements of body temperature, blood pressure, heart rate, and electrocardiogram, monitoring of adverse events at multiple time points during the study.

Efficacy analysis included 24 subjects (Males=17; Females=7; Age: 32.75±6.68 years) who received single dose of CAP 100 mg (2 mg total capsaicinoids) and placebo in a cross-over fashion with a washout period of 3-6 days as per randomization schedule. CAP ingestion significantly ($p<0.05$) increased REE, VO2 & VCO2 at 1, 2 & 3 hours as compared to placebo. VCO2 was also significantly increased at 4-hour post-dose. Further, a subgroup of overweight subjects showed significantly ($p<0.05$) higher REE, VO2 & VCO2 changes at several time points for CAP as compared to placebo. No safety issues or adverse events were observed.

In agreement with our previous study, our current study results further reaffirms increased REE in response to CAP supplementation in healthy human volunteers and supports the use of CAP as a useful nutritional strategy for weight management.

**Keywords:** Metabolism; Capsaicinoids; Obesity; Resting Energy Expenditure

**List of abbreviations:** ASHRAE: American Society of Heating, Refrigerating and Air-Conditioning Engineers; BMI: Body Mass Index; CAP: Capsaicinoid extract; ECG: Electrocardiogram; GCP: Good Clinical Practice; ICH: International Conference on Harmonization; REE: Resting Energy Expenditure

## Introduction

Obesity is a chronic metabolic condition associated with an excess of body fat and may increase the risk of health conditions such as type 2 diabetes, hyperlipidemia, and cardiovascular disease. Worldwide obesity is a serious public health concern affecting 13% of the world population [1] and adult obesity rate is as high as 42% in US alone with an estimated annual medical cost of $148 billion US dollars [2].

Body mass index (BMI) expressed in units of $kg/m^2$ is the measure of body mass divided by the square of the body height and used to define obesity. A BMI of 25.0 to 29.9 is considered as overweight and a BMI of ≥30.0 is considered as obesity. Obesity typically results from energy imbalance [3] due to excessive energy intake and/or insufficient expenditure [3]. Lifestyle changes that include energy intake restriction along with increased physical activity are recommended as part of the weight management strategy. Even a modest weight loss reduces the risk of morbidity and mortality significantly in obese subjects [4-6]. However, sustaining these changes in diet and physical activity are difficult for many and the risk of regaining lost weight is very high [7,8]. Prescription medications used for weight loss have significant undesirable adverse effects and therefore herbal supplements that enhance satiety and boost metabolism are increasingly being used to support weight management [9].

Capsaicinoids are a pungent component of hot peppers and is known to enhance diet-induced energy expenditure, modify energy balance and influence weight management [10-14]. Human and animal studies have consistently demonstrated that capsaicinoids modulate satiety, thermogenesis, energy expenditure, fat oxidation, gut microbiome, glucose and insulin regulation, and blood pressure [15-20]. Further capsaicin induces a significant increase in energy expenditure during exercise when consumed along with the food due to increased carbohydrate oxidation [19]. Capsaicinoids activate brown adipose tissue through transient receptor potential vanilloid 1 (TRPV1), a receptor of the sympathetic nervous system, and increases energy expenditure in mice and humans [21]. Capsaicinoids may also induce thermogenesis via activation of beta-adrenergic receptors as evidenced by reversal of thermogenesis by beta-adrenergic blockers [14,22]. Hence, capsaicinoids have been studied as a potential weight management agent in humans and animals [23,24] and help in reducing abdominal fat in overweight men and women [25].

We developed a proprietary capsicum extract (Capsimax™) obtained from the dried fruits of *Capsicum annum* L. containing 2% total capsaicinoids encapsulated in the form of beadlets. Encapsulation ensures the release of the active content only in the small intestine and avoids oral and gastric burning sensations that may be associated with capsicum extract. Our formulation of CAP was found to be safe and tolerated well at a dose of up to 10 milligrams of capsaicinoids per day [26,27] and shown to reduce appetite, increase free fatty acids and glycerol in the blood, and improve body composition by reducing waist and hip girth and body fat [22, 26-29]. Further, CAP significantly induced higher resting energy expenditure by 6.07% in 40 healthy individuals without significantly changing the heart rate as compared to placebo [33].

The current study evaluated the acute effect of a single dose of CAP on resting energy expenditure (REE) using an indirect calorimetry approach in healthy subjects under fasting condition. Indirect calorimetry is a convenient, reliable, and most widely accepted method of measuring REE that is based on oxygen consumption (VO2) and carbon dioxide production (VCO2) rates [30].

## Materials and Methods

### Study Design and Procedures

The study was designed as a randomized, double-blind, placebo-controlled, cross-over study to assess the safety and efficacy of CAP in healthy adults under fasting condition. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, revised by the WMA General Assembly, Seoul 2008 and Fortalexa 2013) and International Conference on Harmonization (ICH) recommendation on

Good Clinical Practice (GCP) – 2016. The study was approved and monitored by EC – Aditya Independent Ethics Committee, Ahmedabad, Gujarat, India, (ECR/281/Indt/GJ/2017 and OHRP US DHHS Registration Number IRB00011046) to safeguard the rights, safety, and well-being of all trial participants. The study was registered with the clinical trials registry of NIH, "clinicaltrials.gov" bearing NCT No: 04025346.

Subjects visited the study center on day 0 and day 6±2 and were randomized to receive a single dose of CAP or placebo with a washout period of 3 to 6 days to separate the two treatment periods and eliminate any "carry-over" effects. CAP was used at a dose of 100 mg to deliver 2 mg of total capsaicinoids, whereas the placebo was prepared using microcrystalline cellulose. A total of 28 subjects completed the study (Figure 1).

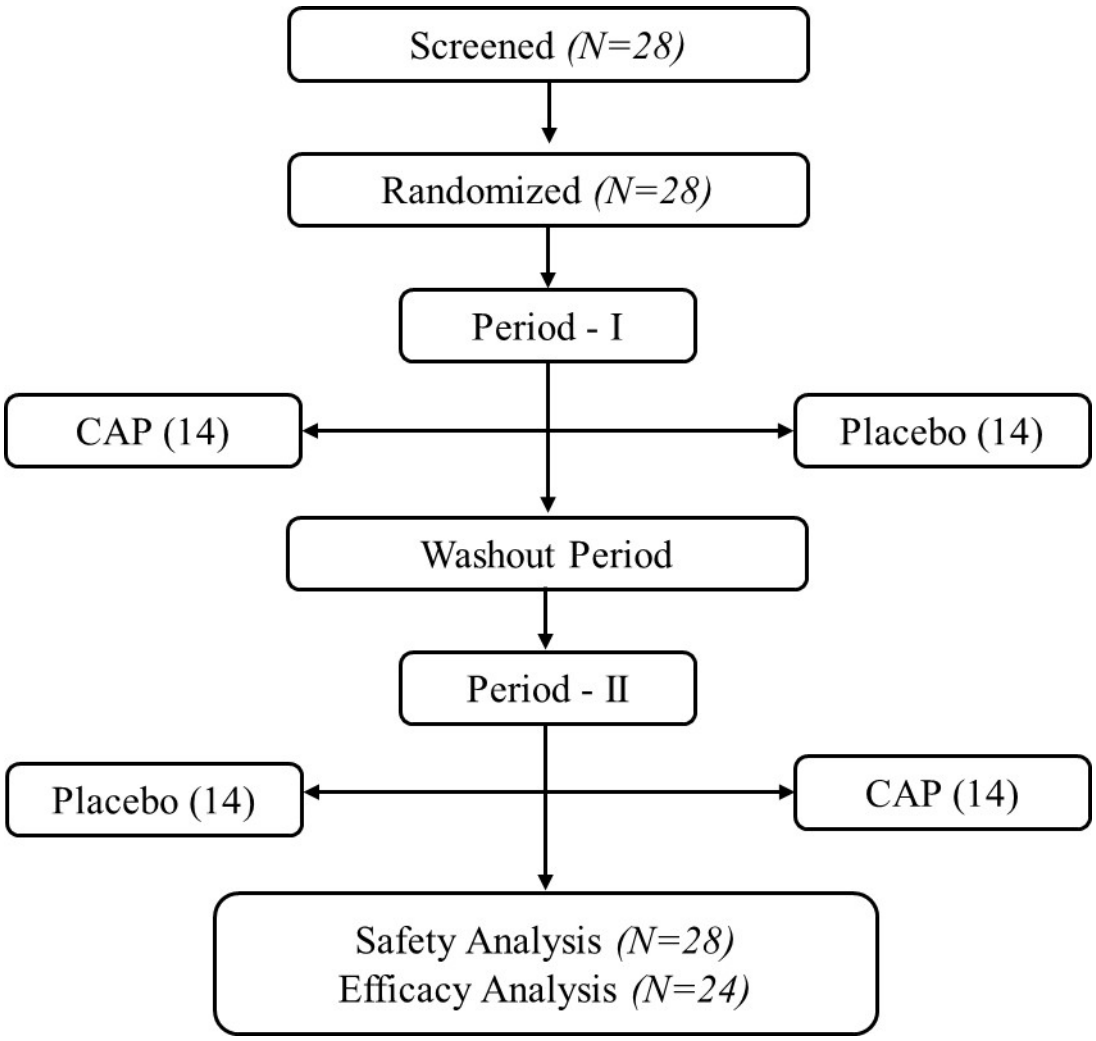


**Figure 1:** Consolidated Standards of Reporting Trials (CONSORT) diagram of clinical trial of CAP vs Placebo

We used Cosmed Q-NRGs (Rome, Italy) [31] metabolic monitor along with canopy hood and oro-nasal face mask to measure REE. The subject's gas exchange collected under spontaneous breathing conditions was used for the calculation of oxygen (VO2) and carbon dioxide volume (VCO2) [31]. The REE analysis was performed on two visit days, day 0 and day 6±2. Subjects were instructed to rest well (at least 7 hours of sleep) and come in a fasting state of 8-12 hours before dosing. During each visit, the measurements were conducted at 0 hours (baseline) before administration of the study product and 1, 2, 3, and 4 hours (+10 minutes) after administration of the study product. The study was conducted with subjects in the supine position, awake, and physically inactive for at least 30±5 minutes to ensure steady levels of VO2 and VCO2 before the collection of data. The entire process lasted for 15 minutes after achieving a steady state. Room temperature was maintained at 23±3° Celsius with less than three individuals present in the room

throughout the study. American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) scale was used to investigate the innate thermal sensation experienced by the individuals after consumption of CAP. ASHRAE scale was administered at 0 hour (pre-consumption) and 0.5, 1, 1.5, 2, 3 and 4 hours post-consumption. The participant was administered the ASHRAE scale and responses were recorded on a Likert scale of +3 (hot) to -3 (cold) at time points as mentioned above. Safety assessments included monitoring of adverse events, physical examination, measurements of vital signs like body temperature, blood pressure, pulse rate, and electrocardiogram at several time points during the study.

## Study Population and Inclusion/Exclusion Criteria

A total of 28 healthy subjects completed the study. Subjects were selected based on the inclusion and exclusion criteria provided in Table 1.

## Statistical Analysis

Statistical analysis has been conducted on the Per Protocol (PP) population. A total of 28 subjects completed the study, four subjects were identified as outliers based on the erratic metabolic response with negative REE at all time points and hence removed from both groups (CAP and Placebo).

Safety analysis was performed for 28 subjects and efficacy analysis was done in 24 subjects (Table 2). Efficacy analysis was also carried out for a subset of subjects who were overweight (BMI of 25.0-29.9 kg/m$^2$).

| **Inclusion criteria** | |
|---|---|
| a. | Healthy, adult, male/female participants with age ≥ 18 to ≤ 55 years |
| b. | Body Mass Index (BMI) between 18.5 to 29.9 kg/m$^2$ |
| c. | Non-smokers |
| d. | Non-alcoholics |
| e. | Given written informed consent to participate in the study |
| f. | Absence of significant disease, clinically significant abnormal medical history, physical examination and systemic examination during the screening |
| g. | Fasting blood sugar ≤ 100 mg/dl (In case the FBS > 100 but ≤ 110 mg/dl, medical monitor's approval will be sought for inclusion of participant in the study) |
| h. | Hemoglobin: Males ≥ 11 g/dL and Females ≥ 10 g/dL |
| i. | LFT: Aspartate aminotransferase (AST)/ Serum Glutamic Oxaloacetic transaminase (SGOT) < 2X Upper normal limit (ULN) and Alanine aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) < 2X ULN |
| j. | BP < 140/90 mmHg |
| k. | Creatinine < 1.5X ULN |
| l. | An ECG without any clinically significant abnormalities |
| m. | Normal TSH within reference range (0.4 - 5.5 μIU/ml) |
| n. | CBC profile without any clinically significant abnormality, based on investigators discretion |
| o. | Participants ready to abstain from caffeinated products for 24 hours prior to visit |
| p. | Participants ready to abstain from strenuous physical activity for 48 hours prior to visit |
| q. | Participants having at least 7 hours of sleep on the night prior the day of assessment |
| r. | Normal pulmonary function test with normal expiratory volume with no other abnormality |
| s. | Compliance with the requirement of the entire protocol |
| t. | Participants willing to follow all study procedures and follow up visits |
| u. | Females with ongoing menstruation at randomization were rescreened after completion of menstrual cycle, if they were out of the allotted window period |

| Exclusion criteria |
|---|
| a. Institutionalized participants |
| b. History of hypersensitivity to chilies |
| c. History of ulcers, piles or fistula, abdominal pain, and any other digestive disorders |
| d. History or evidence of chronic diseases such as diabetes, hypertension, liver disorders, kidney disorders, pulmonary disease or infections, cardiovascular disease, pancreatic disease, infectious diseases, dermatological problems, arthritis, and any cancer |
| e. History of hypo or hyperthyroidism |
| f. Signs or symptoms of acute illness, which includes fever, inflammation, allergic rash or sudden pain on the day of assessment |
| g. Clinical conditions that may jeopardize the study outcome such as gastrointestinal bleeding, history of unintentional weight loss in the last 3 months, anemia, dysphagia, or abdominal mass |
| h. History of a significant neurological or psychiatric condition such as seizures, depression, etc., |
| i. History of sleep insufficiency/ disorders including insomnia |
| j. Habit of consuming high caffeine (more than 5 cups of coffee or tea/day) consumption |
| k. Current use of vitamins, supplements or medications known to influence chronic disease/condition |
| l. History of addiction to any recreational drug or drug dependence |
| m. Donation of blood (1 unit or 350 mL) within 90 days prior to study dosing |
| n. Participation in any clinical study within the past 90 days before dosing |
| o. Pregnant/planning to be pregnant during the study period, lactating, or women of childbearing potential who are unwilling to commit to the use of a medically approved form of contraception throughout the study period |
| p. Any other condition, which in the opinion of the investigator may jeopardize the study |

**Table 1:** Inclusion and exclusion criteria for subject selection into the study

| | Mean (SD) | Min, Max |
|---|---|---|
| **Age (in completed years)** | 32.75 (6.68) | 22 – 44 |
| **BMI (kg/m$^2$)** | 24.67 (2.83) | 19.55 – 29.67 |
| **Gender (%)** | | |
| **Male** | 20 (71.4) | |
| **Female** | 08 (28.6) | |

BMI - Body Mass Index; Min. - Minimum; Max. - Maximum

**Table 2:** Summary of participant demographic characteristics (N=28)

The study data was analyzed in a blinded manner as per the statistical analysis plan. The data normality distribution was evaluated using the Shapiro-Wilk test. The parameters REE, VO2, VCO2 and ASHRAE score were analyzed using Type III sum of squares, with the main effects of formulation, period, sequence and subjects nested within sequence. A separate ANOVA model were used to analyze each of the parameters. The sequence effect was tested at the 10% level of significance using the subjects nested within sequence mean square as the error term. Formulation and period effects were tested at the 5% level of significance against the residual error (mean square error) from the ANOVA model as the error term. Each analysis of variance included calculation of least-squares means, the difference between the adjusted formulation means and the standard error associated with the difference. The statistical analyses were conducted using SAS® version 9.4.

## Results

The study population comprised of 20 males (71.40%) and 8 females (28.60%) with a mean age of 32.75±6.68 years and mean BMI of 24.67±2.83 Kg/m$^2$.

## Change in Resting Energy Expenditure

### All subjects

REE was calculated for each time point as a difference from baseline. CAP consumption showed a significant ($p<0.05$) increase in REE at 1 hour (149.05 kcal/day), 2 hours (104.19 kcal/day), 3 hours (93.94 kcal/day), and an increasing trend at 4 hours (65.33 kcal/day; $p=0.06$) as compared to placebo. There was a significant increase in average REE by 104.48 kcal/day (7.07%) as compared to placebo.

### Overweight subjects

In overweight subjects, CAP group showed a significant ($p<0.05$) increase in REE at 1 hour (217.60 kcal/day) and 2 hours (143.34 kcal/day), a non-significant ($p>0.05$) increase in REE at 3 hours (55.93 kcal/day) and 4 hours (91.34 kcal/day) with a significant increase in average REE by 128.93 kcal/day (8.86%) as compared to placebo.

Figure 2 and Table 3 summarizes the REE data for all subjects and overweight subjects.

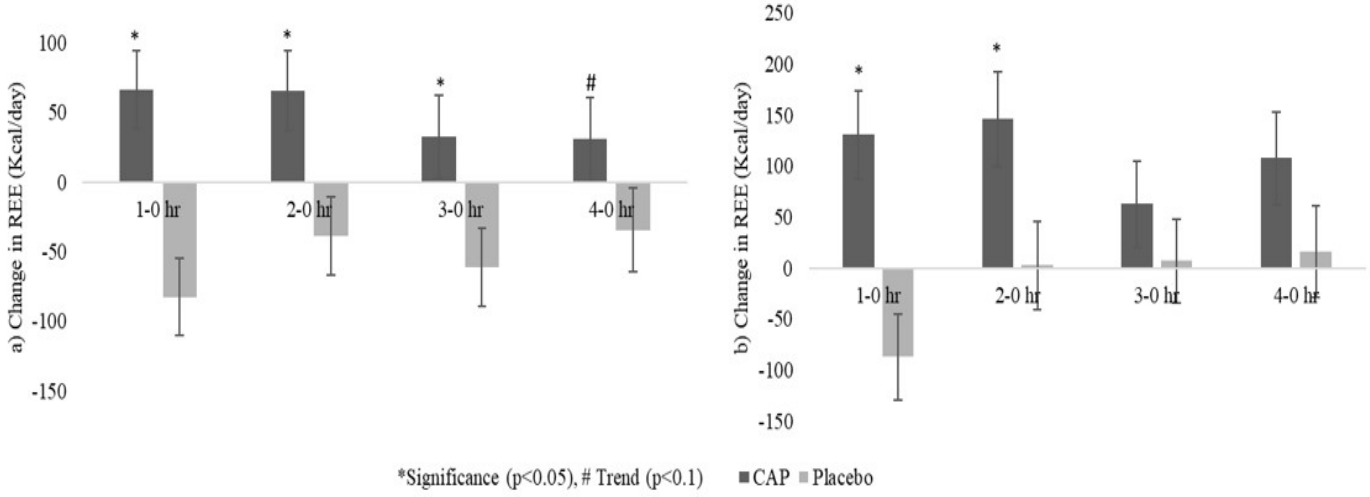


**Figure 2:** Summary of change in Resting Energy Expenditure (REE) (Kcal/day) of all subjects **(A);** and overweight subjects **(B)** between CAP and placebo.

## Change in Oxygen Consumption Rate (VO2)

### All subjects

VO2 was calculated for each time point as a difference from baseline. CAP consumption showed significant ($p<0.05$) increase in VO2 at 1 hour (1.01 ml/kg/min), 2 hours (0.70 ml/kg/min) and 3 hours (0.57 ml/kg/min), a non-significant ($p>0.05$) increase in VO2 at 4 hours (0.30 ml/kg/min) and a statistically significant increase in average VO2 by 0.65 ml/kg/min (7.14%) as compared to placebo.

### Overweight subjects

In overweight subjects, CAP group showed significant ($p<0.05$) increase in VO2 at 1 hour (1.49 ml/kg/min) and 2 hours (0.96 ml/kg/min), non-significant ($p>0.05$) increase in VO2 at 3 hours (0.28 ml/kg/min) & 4 hours (0.42 ml/kg/min) and a trend (p-value=0.06) increase in average VO2 by 0.88 ml/kg/min (8.84%) as compared to placebo. Figure 3 and Table 4 summarizes VO2 data for all subjects and overweight subjects.

| Time point (hr) | All subjects (N=24) | | | | | | | Overweight subjects (N=13) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (P) | | CAP (C) | | LS Mean change difference from 0 hr (C-P) (SE) | LS Mean change difference from 0 hr (C-P) % | P-value | Placebo (P) | | CAP (C) | | LS Mean change difference from 0 hr (C-P) (SE) | LS Mean change difference from 0 hr (C-P) % | P-value |
| | LS Mean REE (SE) | LS Mean change from 0 hr (SE) | LS Mean REE (SE) | LS Mean change from 0 hr (SE) | | | | LS Mean REE (SE) | LS Mean change from 0 hr (SE) | LS Mean REE (SE) | LS Mean change from 0 hr (SE) | | | |
| 0 hr | 1553.05 (46.93) | - | 1487.63 (46.93) | - | - | - | - | 1613.69 (76.27) | - | 1525.86 (76.27) | - | - | - | - |
| 1 hr | 1470.36 (49.80) | -82.69 (27.65) | 1550.90 (50.12) | 66.36 (28.17) | 149.05 (39.47) | 10.03 | 0.0011* | 1526.70 (76.77) | -86.99 (41.98) | 1651.09 (77.51) | 130.61 (43.12) | 217.60 (60.17) | 14.74 | 0.0047* |
| 2 hr | 1514.45 (50.14) | -38.60 (28.07) | 1556.48 (50.58) | 65.58 (28.82) | 104.19 (39.21) | 7.18 | 0.0147* | 1616.54 (73.69) | 2.85 (43.16) | 1672.93 (76.38) | 146.19 (46.37) | 143.34 (63.35) | 10.03 | 0.0471* |
| 3 hr | 1484.53 (51.69) | -61.23 (28.11) | 1524.10 (52.54) | 32.71 (29.71) | 93.94 (31.08) | 6.52 | 0.0077* | 1608.98 (85.59) | 7.01 (41.33) | 1592.78 (86.07) | 62.94 (42.04) | 55.93 (32.90) | 4.10 | 0.1275 |
| 4 hr | 1517.70 (46.28) | -34.58 (30.22) | 1515.54 (46.28) | 30.75 (30.22) | 65.33 (32.47) | 4.56 | 0.0579# | 1628.50 (68.50) | 16.22 (45.19) | 1624.39 (68.50) | 107.56 (45.19) | 91.34 (57.03) | 6.57 | 0.1437 |
| Average | - | -53.86 (24.26) | - | 50.62 (24.26) | 104.48 (31.45) | 7.07 | 0.0031* | - | -16.26 (36.08) | - | 112.68 (36.08) | 128.93 (50.11) | 8.86 | 0.0259* |

CAP: Capsimax™; SE: Standard Error

LS Means, SE, Difference and P-value from the mixed effect model MMRM on the change from 0 hr of VO2. The model includes group, time point and group-by-time point interaction as fixed effects.

*Significance $p<0.05$, # Trend ($p<0.1$)

**Table 3:** Summary of between group analysis for Resting Energy Expenditure

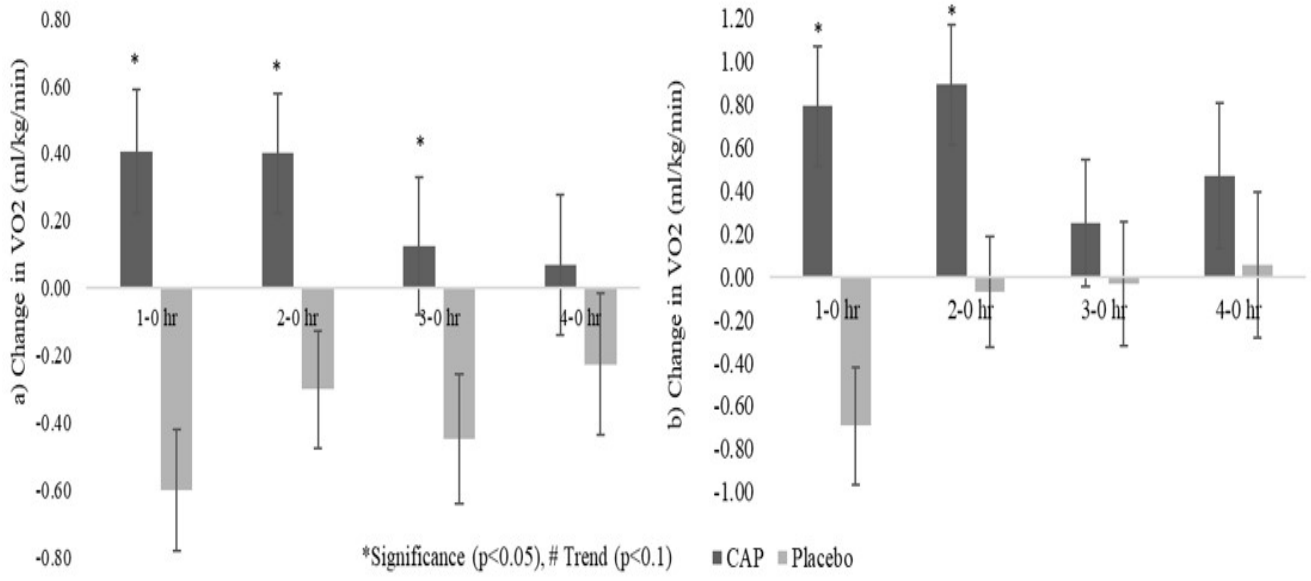


**Figure 3:** Summary of change in Oxygen Consumption Rate - VO2 (ml/kg/min) of all subjects **(A);** and overweight subjects **(B)** between CAP and placebo.

| Time point (hr) | All subjects (N=24) | | | | | | | Overweight subjects (N=13) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (P) | | CAP (C) | | LS Mean change difference From 0 hr (C-P) (SE) | LS Mean change difference From 0 hr (C-P) % | P-value | Placebo (P) | | CAP (C) | | LS Mean change difference from 0 hr (C-P) (SE) | LS Mean change difference From 0 hr (C-P) % | P-value |
| | LS Mean VO2 (SE) | LS Mean change from 0 hr (SE) | LS Mean VO2 (SE) | LS Mean change from 0 hr (SE) | | | | LS Mean VO2 (SE) | LS Mean change from 0 hr (SE) | LS Mean VO2 (SE) | LS Mean change from 0 hr (SE) | | | |
| 0 hr | 9.51 (0.33) | - | 9.11 (0.33) | - | - | - | - | 9.86 (0.56) | - | 9.44 (0.56) | - | - | - | - |
| 1 hr | 8.91 (0.34) | -0.60 (0.18) | 9.49 (0.35) | 0.41 (0.18) | 1.01 (0.26) | 10.89 | 0.0008* | 9.16 (0.55) | -0.69 (0.27) | 10.19 (0.55) | 0.79 (0.28) | 1.49 (0.39) | 16.16 | 0.0035* |
| 2 hr | 9.21 (0.34) | -0.30 (0.17) | 9.57 (0.35) | 0.40 (0.18) | 0.70 (0.23) | 7.73 | 0.0062* | 9.79 (0.51) | -0.07 (0.26) | 10.45 (0.52) | 0.89 (0.28) | 0.96 (0.38) | 10.69 | 0.0288* |
| 3 hr | 9.01 (0.35) | -0.45 (0.19) | 9.30 (0.36) | 0.12 (0.20) | 0.57 (0.22) | 6.45 | 0.0187* | 9.73 (0.58) | -0.03 (0.29) | 9.79 (0.58) | 0.25 (0.29) | 0.28 (0.24) | 3.26 | 0.2698 |
| 4 hr | 9.26 (0.31) | -0.23 (0.21) | 9.16 (0.31) | 0.068 (0.21) | 0.30 (0.22) | 3.48 | 0.2034 | 9.89 (0.48) | 0.05 (0.34) | 9.85 (0.48) | 0.47 (0.34) | 0.42 (0.40) | 5.25 | 0.3209 |
| Average | - | -0.37 (0.18) | - | 0.28 (0.20) | 0.65 (0.23) | 7.14 | 0.0127* | - | -0.16 (0.29) | - | 0.72 (0.33) | 0.88 (0.37) | 8.84 | 0.0648# |

CAP: Capsimax™; SE: Standard Error

LS Means, SE, Difference and P-value from the mixed effect model MMRM on the change from 0 hr of VO2.

The model includes group, time point and group-by-time point interaction as fixed effects.

*Significance $p<0.05$, # Trend ($p<0.1$)

**Table 4:** Summary of between group analysis for VO2

## Change in Carbon dioxide Production Rate (VCO2)

### All subjects

VCO2 was calculated for each time point as a difference from baseline. CAP consumption showed significant ($p<0.05$) increase in VCO2 at 1 hour (0.71 ml/kg/min), 2 hours (0.61 ml/kg/min), 3 hours (0.67 ml/kg/min) and 4 hours (0.56 ml/kg/min) post-dose and a statistically significant increase in average VCO2 by 0.58 ml/kg/min (6.76%) as compared to placebo.

### Overweight subjects

In case of overweight subjects, CAP showed significant ($p<0.05$) increase in VCO2 at 1 hour (1.04 ml/kg/min) and 2 hours (0.85 ml/kg/min), increasing trend at 3 hours (0.65 ml/kg/min; p-value= 0.07), a non-significant ($p>0.05$) increase at 4 hours (0.68 ml/kg/min) and a non-significant increase in average VCO2 by 0.73 ml/kg/min (8.50%) as compared to placebo.

Figure 4 and Table 5 summarize VCO2 data for all subjects and overweight subjects.

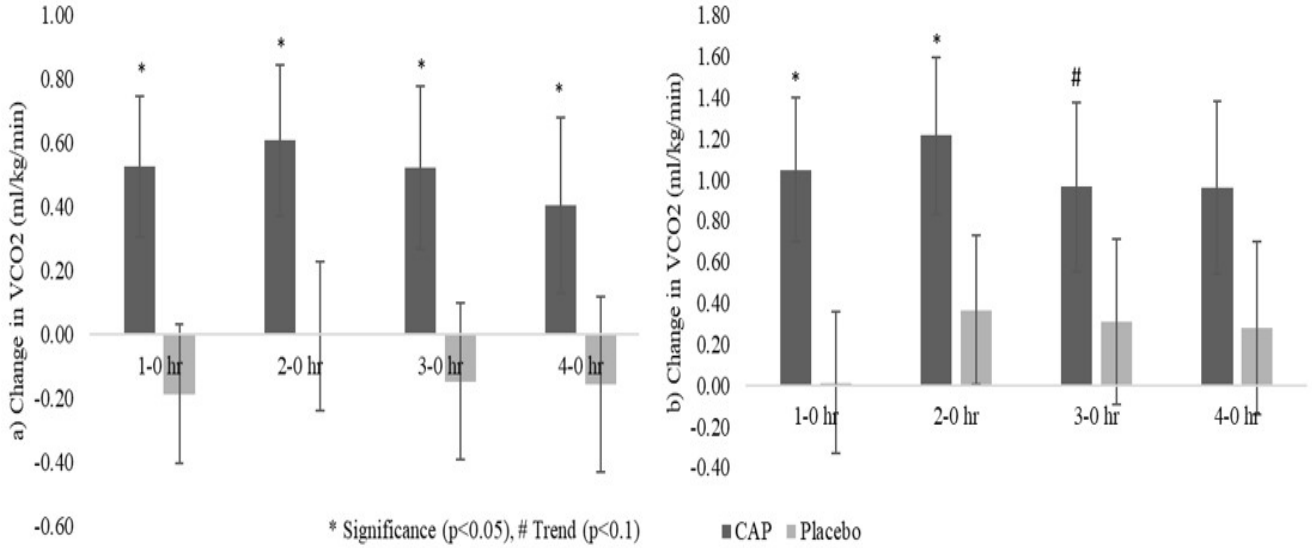


**Figure 4:** Summary of change in Carbon dioxide Production Rate - VCO2 (ml/kg/min) of all subjects **(A);** and overweight subjects **(B)** between CAP and placebo.

| Time point (hr) | All subjects (N=24) | | | | | | | Overweight subjects (N=13) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (P) | | CAP (C) | | LS Mean change difference from 0 hr (C-P) (SE) | LS Mean change difference from 0 hr (C-P) % | P-value | Placebo (P) | | CAP (C) | | LS Mean change difference from 0 hr (C-P) (SE) | LS Mean change difference From 0 hr (C-P) % | P-value |
| | LS Mean VCO2 (SE) | LS Mean change from 0 hr (SE) | LS Mean VCO2 (SE) | LS Mean change from 0 hr (SE) | | | | LS Mean VCO2 (SE) | LS Mean change from 0 hr (SE) | LS Mean VCO2 (SE) | LS Mean change from 0 hr (SE) | | | |
| 0 hr | 9.71 (0.32) | - | 9.41 (0.32) | - | - | - | - | 10.02 (0.52) | - | 9.73 (0.52) | - | - | - | - |
| 1 hr | 9.53 (0.43) | -0.19 (0.22) | 9.91 (0.44) | 0.53 (0.22) | 0.71 (0.29) | 7.51 | 0.0236* | 10.03 (0.70) | 0.01 (0.34) | 10.73 (0.71) | 1.05 (0.35) | 1.04 (0.44) | 10.83 | 0.0406* |
| 2 hr | 9.71 (0.44) | -0.00 (0.23) | 10.07 (0.45) | 0.61 (0.24) | 0.61 (0.24) | 6.57 | 0.0183* | 10.39 (0.70) | 0.37 (0.36) | 11.04 (0.71) | 1.22 (0.38) | 0.85 (0.36) | 8.96 | 0.042* |
| 3 hr | 9.50 (0.46) | -0.15 (0.24) | 9.94 (0.47) | 0.52 (0.25) | 0.67 (0.21) | 6.98 | 0.0056* | 10.23 (0.79) | 0.31 (0.40) | 10.69 (0.80) | 0.96 (0.41) | 0.65 (0.32) | 6.92 | 0.0716# |
| 4 hr | 9.57 (0.45) | -0.16 (0.28) | 9.83 (0.45) | 0.41 (0.28) | 0.56 (0.23) | 6.00 | 0.0235* | 10.32 (0.73) | 0.28 (0.42) | 10.71 (0.73) | 0.96 (0.42) | 0.68 (0.38) | 7.30 | 0.1095 |
| Average | - | -0.13 (0.23) | - | 0.46 (0.25) | 0.58 (0.24) | 6.76 | 0.031* | - | 0.25 (0.39) | - | 0.98 (0.44) | 0.73 (0.42) | 8.50 | 0.1443 |

CAP: Capsimax™; SE: Standard Error

LS Means, SE, Difference and P-value from the mixed effect model MMRM on the change from 0 hr of VCO2. The model includes group, time point and group-by-time point interaction as fixed effects.

*Significance p<0.05, # Trend (p<0.1)

**Table 5:** Summary of between group analysis for VCO2

**Change in ASHRAE scores**

Administration of CAP showed a feeling of warmth at 30 minutes as an increasing trend (difference=0.32 units; p=0.05) for all subjects and non-significant increase in overweight subjects as compared to the placebo group. CAP supplementation showed a non-significant increase in a feeling of warmth at all other time points i.e., 1, 1.5, 2, 3 and 4 hrs as compared to placebo.

Figure 5 and Table 6 summarize ASHRAE data for all subjects and overweight subjects.

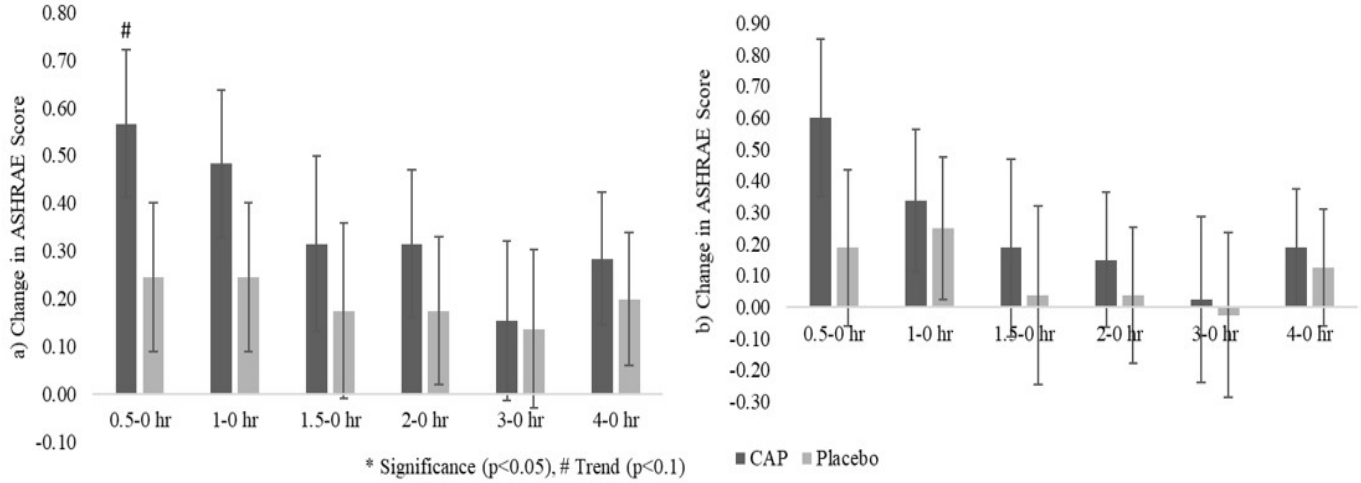


**Figure 5:** Summary of change in ASHRAE scores of all subjects **(A);** and overweight subjects **(B)** between CAP and placebo.

| Time point (hr) | All subjects (N=24) | | | | | | Overweight subjects (N=13) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (P) | | CAP (C) | | LS Mean change difference from 0 hr (C-P) (SE) | P-value | Placebo (P) | | CAP (C) | | LS Mean change difference from 0 hr (C-P) (SE) | P-value |
| | LS Mean ASHRAE (SE) | LS Mean change from 0 hr (SE) | LS Mean ASHRAE (SE) | LS Mean change from 0 hr (SE) | | | LS Mean ASHRAE (SE) | LS Mean change from 0 hr (SE) | LS Mean ASHRAE (SE) | LS Mean change from 0 hr (SE) | | |
| 0 hr | -0.10 (0.12) | - | -0.16 (0.12) | - | - | - | -0.14 (0.21) | - | -0.13 (0.21) | - | - | - |
| 0.5 hr | 0.15 (0.17) | 0.24 (0.16) | 0.41 (0.17) | 0.57 (0.16) | 0.32 (0.16) | 0.0521# | 0.05 (0.29) | 0.19 (0.25) | 0.48 (0.29) | 0.60 (0.25) | 0.41 (0.28) | 0.1698 |
| 1 hr | 0.15 (0.15) | 0.24 (0.16) | 0.32 (0.15) | 0.48 (0.16) | 0.24 (0.16) | 0.1596 | 0.11 (0.24) | 0.25 (0.22) | 0.21 (0.24) | 0.34 (0.22) | 0.09 (0.22) | 0.7011 |
| 1.5 hr | 0.08 (0.18) | 0.17 (0.18) | 0.15 (0.18) | 0.31 (0.18) | 0.14 (0.14) | 0.3419 | -0.10 (0.31) | 0.04 (0.28) | 0.06 (0.31) | 0.19 (0.28) | 0.15 (0.22) | 0.5171 |
| 2 hr | 0.08 (0.15) | 0.17 (0.16) | 0.15 (0.15) | 0.31 (0.16) | 0.14 (0.16) | 0.3816 | -0.10 (0.24) | 0.04 (0.21) | 0.03 (0.24) | 0.15 (0.21) | 0.11 (0.26) | 0.6723 |
| 3 hr | 0.04 (0.16) | 0.14 (0.17) | -0.01 (0.16) | 0.15 (0.17) | 0.02 (0.16) | 0.9124 | -0.16 (0.28) | -0.03 (0.26) | -0.10 (0.28) | 0.03 (0.26) | 0.05 (0.26) | 0.8514 |
| 4 hr | 0.10 (0.15) | 0.20 (0.14) | 0.12 (0.15) | 0.28 (0.14) | 0.08 (0.18) | 0.6535 | -0.01 (0.23) | 0.13 (0.19) | 0.06 (0.23) | 0.19 (0.19) | 0.06 (0.26) | 0.8166 |

CAP: Capsimax™; SE: Standard Error

LS Means, SE, Difference and P-value from the mixed effect model MMRM on the change from 0 hr of VCO2. The model includes group, time point and group-by-time point interaction as fixed effects.

*Significance p<0.05, # Trend (p<0.1)

**Table 6:** Summary of between group analysis for ASHRAE score

## Safety

No safety concerns were observed for various safety parameters measured such as ECG, systolic and diastolic blood pressure, and heart rate based on a comparison between CAP and placebo groups ($p>0.05$). Two adverse events were reported in the CAP group which included backache and diarrhea. The placebo group also experienced adverse events, specifically headache and general body pain (Table 7). None of the adverse events were severe and related to CAP.

Table 8 summarizes blood pressure and pulse rate data for all subjects and overweight subjects. The safety analysis results are illustrated in Figure 6.

| | CAP (N=28) | | Placebo (N=28) | | All (N=28) | |
|---|---|---|---|---|---|---|
| **AEs** | **n** | **%** | **n** | **%** | **n** | **%** |
| Headache | 0.00 | 0.00 | 1.00 | 3.57 | 1.00 | 3.57 |
| Backache | 1.00 | 3.57 | 0.00 | 0.00 | 1.00 | 3.57 |
| General body pain | 0.00 | 0.00 | 1.00 | 3.57 | 1.00 | 3.57 |
| Diarrhoea | 1.00 | 3.57 | 0.00 | 0.00 | 1.00 | 3.57 |

n/% = Number / percentage of participants reporting at least once a specified symptom during the treatment period

**Table 7:** Summary of adverse events

| Time point (hr) | Mean (SD) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BP systolic (mm Hg) (N=28) | | | | | BP diastolic (mm Hg) (N=28) | | | | | Pulse Rate (beats/minute) (N= 28) | | | | |
| | Placebo (P) | CAP (C) | Min - Max (P) | Min - Max (C) | P-value | Placebo (P) | CAP (C) | Min - Max (P) | Min - Max (C) | P-value | Placebo (P) | CAP (C) | Min - Max (P) | Min - Max (C) | P-value |
| 0 hr | 125.14 (5.35) | 122.96 (7.13) | 110 - 134 | 110 - 134 | 0.258 | 76.43 (6.72) | 77.57 (6.09) | 62 - 90 | 68 - 90 | 0.563 | 73.71 (8.4) | 73.71 (8.25) | 55 - 90 | 50 - 88 | 0.948 |
| 1 hr | 124.86 (6.43) | 123 (5.75) | 110 - 140 | 110 - 132 | 0.337 | 78.07 (8.32) | 78.29 (4.95) | 62 - 94 | 68 - 90 | 0.619 | 67.93 (8.51) | 69.68 (7.49) | 52 - 92 | 51 - 82 | 0.236 |
| 2 hr | 123.29 (5.74) | 122.50 (6.00) | 112 - 136 | 110 - 134 | 0.741 | 76.43 (8.14) | 76.93 (5.59) | 60 - 92 | 64 - 90 | 0.692 | 68.68 (7.36) | 68.64 (6.82) | 51 - 88 | 52 - 84 | 0.857 |
| 3 hr | 124.57 (5.73) | 122.50 (5.24) | 114 - 140 | 114 - 132 | 0.139 | 76.79 (7.53) | 75.54 (6.76) | 60 -92 | 64 - 90 | 0.541 | 68.18 (8.61) | 68.39 (7.40) | 50 - 89 | 51 - 84 | 0.774 |
| 4 hr | 125.11 (6.67) | 122.79 (6.12) | 112 - 140 | 110 - 138 | 0.244 | 76.39 (6.81) | 76.86 (5.77) | 64 - 94 | 64 - 90 | 0.656 | 67.36 (6.62) | 67.68 (6.83) | 54 - 80 | 53 - 81 | 0.934 |

CAP-Capsimax™; SD: Standard Deviation

List of abbreviations: hr: Hours; SD: Standard deviation; Min: Minimum; Max: Maximum; N: number of participants

Test of Significance - Mann Whitney U Test

**Table 8:** Summary of safety analysis - blood pressure and pulse rate

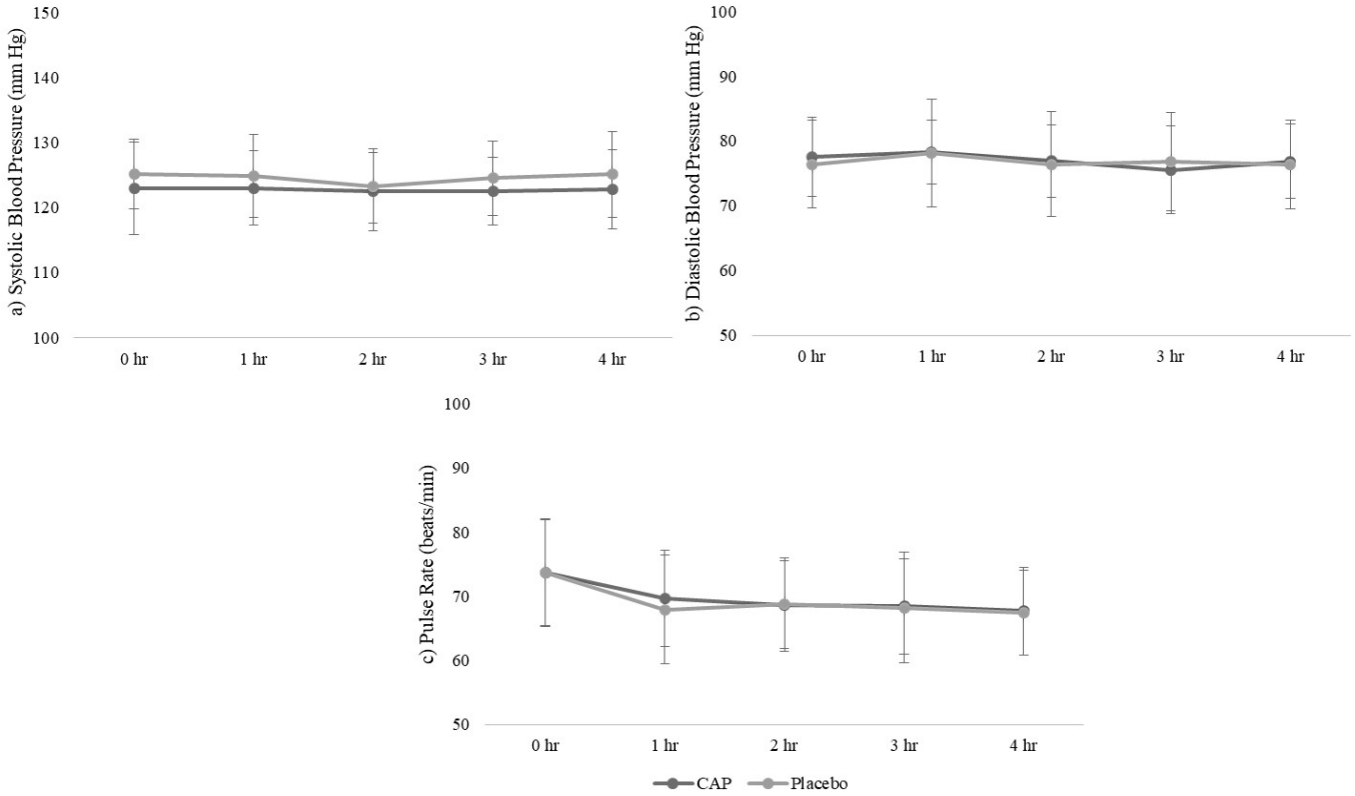


**Figure 6:** Summary of change in **(A)** systolic blood pressure (mmHg); **(B)** diastolic blood pressure (mmHg); and **(C)** pulse rate (beats/minute) between CAP and placebo. Analysis was performed using Mann Whitney U Test

## Discussions

Capsaicinoids from chili pepper are known to enhance thermogenesis [22] and increase REE. REE which is the basal metabolic rate at resting state plays an important role in energy homeostasis and hence body weight management [32]. In the past study, we have demonstrated CAP-induced enhancement of REE in healthy adult volunteers under fed state using Breezing, a handheld device to monitor metabolic rate [33]. In the current study, we used the Cosmed Q-NRG metabolic monitor, which is gold standard for measurement of basal metabolic rate, to measure CAP-induced resting energy expenditure in fasting healthy volunteers. The study results reconfirmed our previous study [33] that CAP at a dose of 2 mg of total capsaicinoids significantly increased REE in healthy subjects along with increased VO2 and VCO2.

We demonstrate that administration of a single dose of CAP increased REE values from baseline at 1, 2 and 3 hours post-dose in all subjects which was statistically significant ($p<0.05$) as compared to placebo with an average REE increase of 104.48 kcal/day. Further in case of overweight subjects we observed a higher response against CAP with a significant ($p<0.05$) increase in REE at 1 and 2 hours post-dose and an average increase in REE of 128.93 kcal/day when compared to placebo. Overweight or obese people burn more calories due to higher energy requirements which might have contributed to the higher REE response observed in our study.

Capsaicinoids increase oxygen consumption [34,35] in mice and human volunteers [36] and are associated with enhanced REE and fat oxidation [37]. We observed a significant ($p<0.05$) increase in VO2 at 1, 2 & 3 hours in response to CAP consumption as compared to placebo which was found to be further enhanced in overweight subjects. The findings of increased VO2 here are relevant and meaningful as it mediates the increase in REE and fat oxidation which in turn may help individuals trying to manage their body weight.

We also observed that CAP consumption significantly ($p<0.05$) increased the amount of carbon dioxide exhaled from the body

per unit time as compared to the placebo group at all time points measured in the study. Again, subset analysis with the overweight subjects showed significantly higher VCO2 in response to CAP consumption.

All subjects who received a single dose of CAP showed an increasing trend of feeling of warmth measured by ASHRAE score (p=0.05) when compared to placebo after 30 minutes which supports an experiential effect felt by study participants due to the thermogenic effect of CAP. No discomfort was reported by the study participants as evaluated by the ASHRAE score. Cardiovascular parameters measured such as QT interval, ECG, blood pressure, body temperature, and pulse rate remained normal. CAP was tolerated well with no adverse events observed related to gastric discomfort.

Josse et al., (2010), demonstrated that ingestion of 10 mg of capsaicinoids 30 minutes before exercise elevated VO2, lipid peroxidation, and increased catecholamine levels leading to increased metabolic rate and lipid oxidation consistent with activation of the adrenergic system [38]. Most of the other studies demonstrated increased REE in response to combination products such as green tea catechins, caffeine, and calcium [39] or green tea and caffeine [40]. We recorded a significant increase in REE in response to a single dose of 2 mg of total capsaicinoids which is 7.1% for the overall group and 8.9% for overweight subjects as compared to placebo. The overall findings of increased REE further revalidates our similar data from previous study [33]. We observed higher increase in REE in case of overweight subjects which could be due to their higher body size which requires more energy for maintenance and hence higher basal metabolic rate [41]. The changes in REE that we observed in response to CAP are meaningful as REE accounts for 60-75% of the calories burnt by an individual per day and thus play a significant role in energy homeostasis. One of the study limitations was that the study was conducted in an acute dose setting to evaluate the effect of CAP on resting energy expenditure. A longer-term study should be conducted to demonstrate the effects of chronic supplementation with CAP on REE.

## Conclusions

In conclusion, we demonstrate that CAP increased REE by 104.48 kcal/day (7.07%) in all subjects and 128.93 kcal/day (8.86%) in overweight subjects as compared to placebo – these are meaningful changes in in energy expenditure. Further, we also demonstrate CAP as a safe, plant-based dietary supplement to enhance metabolism, induction of thermogenesis and support weight management.

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