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Capsaicinoids Enhance Metabolic Rate in Normal Healthy Individuals using a Novel Metabolic Tracker Breezing Device-An Open Label Placebo Controlled Acute Study

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Abstract

Increasing daily energy expenditure (EE) plays an important role for metabolic health and weight management. Obesity, an epidemic with associated conditions has kept increasing in all age groups for the past three decades. There is no evidence of a decline in overweight and obesity prevalence in any age group for the past 10 years. Capsaicinoids are bioactives from Capsicum extract reported lipolysis, increased energy expenditure, increased lipid oxidation and reduced appetite. Breezing[®] is a portable device that measures your metabolism using a method called indirect calorimetry. It analyzes your rates of oxygen consumption and carbon dioxide production. Breezing[®], a handheld device about the size of a computer mouse, is the world's first battery-operated portable metabolism tracker that syncs with a smartphone. This innovative device helps people develop a personalized weight management plan based on their own metabolic profile. Resting energy expenditure (REE) affected by factors such as body composition, age, sex, medical conditions and genetics. The purpose of this study is to investigate the effects of capsaicinoids supplement on metabolic rate and heart rate upon the supplementation at rest in healthy subjects. In a single blind, acute, placebo-controlled, crossover open label study and after an initial familiarization visit, 40 subjects (male: n=23; female: n=17; Age: 28.2 ± 5.3 y; body mass index=23.1 ± 3.8lb/in²; Body fat (Bio-impedence): 18.6 ± 7.2%) underwent testing sessions with metabolic tracker breezing equipment during which time they consumed either a 2 mg capsaicinoids supplement (100 mg Capsimax[®]) or placebo, one capsule per day. At least 35 subjects are required to satisfy a power of 0.95 with an α of 0.05. After supplementation, resting energy expenditure (REE) at different time points (Baseline (BL), 1 h, 2 h and 3 hrs and calculated for 24 hr REE), heart rate (HR), and blood pressure (BP) were assessed. The capsaicinoids treatment resulted in significantly ($p \leq 0.05$) greater energy expenditure [Δ REE% 6.07] vs. placebo. The extrapolated REE changes in 24 hrs for capsaicinoids were 130 kcal/day (7.23%) and placebo was 8 kcal/day (1.17%). There were no significant between-treatment differences for Heart rate (HR). These findings indicate that the thermogenic nutritional supplement could increase resting energy expenditure (REE). Further long term studies are required to explore breezing metabolic tracker use in nutritional studies for weight management.

Keywords: Metabolic rate; Capsaicinoids; Energy Expenditure; Thermogenesis**Abbreviations:** CAPs: Capsaicinoids; REE: Resting Energy Expenditure; EE: Energy Expenditure; HR: Heart rate; BP: Blood pressure; BL: Baseline; VO₂: Oxygen Consumption Rate; VCO₂: Carbon dioxide Production Rate; RQ: Respiratory Quotient

Introduction

Obesity is an epidemic in U.S and may lead to risk of hypertension, diabetes and cardiovascular disease [1]. Obesity significantly increases risk of death from hypertension, stroke, diabetes, osteoarthritis, coronary heart disease, gallbladder disease, sleep apnea and respiratory problems, and endometrial, breast, prostate, and colon cancers and other associated clinical conditions [2]. Nearly 2.1 billion people of the world's population – are either obese or overweight [3,4]. Obesity is often considered to be a result of either excessive food intake or of insufficient energy expenditure [5].

Capsaicinoids are the major pungent, naturally occurring active compounds in capsicum fruits such as hot chili peppers (genus capsicum), with the most abundant forms being capsaicin, dihydrocapsaicin, and nordihydrocapsaicin [6]. The available information indicates that capsaicinoids possess a wide variety of biological and physiological activities, including anti-inflammatory [7], antioxidant, and anti-cancer [8]. Whiting et al. [9,10] indicated that capsaicinoids play a beneficial role, as part of a weight management program. Capsaicinoids (CAPs) are found in chili peppers and their extracts. They have been reported

to increase thermogenesis [11-13] and decrease chances of obesity [14]. Indirect calorimetry is a noninvasive and reliable means of determining resting metabolic rate in humans. Resting energy expenditure (REE) is the basic metabolic rate a resting state and represents the minimum energy needed to sustain life [15]. It is one of the key factors for weight management. Different methods have been developed to measure REE. Recently a mobile indirect calorimeter called Breezing[®] was developed to facilitate personalized REE measurement. Based on optical detection of a chemical sensor cartridge [16], oxygen consumption rate (VO₂) and carbon dioxide production rate (VCO₂) in breath was determined. According to the Weir equation [17], REE was determined by VO₂, VCO₂ and breath flow rate, which was measured by a commercial flow sensor implemented inside the device. Thus, the objective of this study was to examine the effect of capsaicinoids supplement (CAPs) on REE using a mobile indirect calorimeter called Breezing[®] device. This study is the first systematic data collection with resolution of 1 h (point-in-time) measurements and observed changes with CAPs acute supplementation. In addition, the study design carefully implemented a customized meal that was administrated as a percentage of the subject's REE baseline measurement.

Subjects and Methods

Participants

Forty healthy adults (N=40), crossover, one week washout, single dose administration, acute study including 23 male and 17 female, were tested in this study. Inclusion criteria included: age within the range 22-47 years, and free living population and their body mass index ranged from 18.1 to 32.8 lb/in², as summarized in Table 1. Exclusion criteria included: pregnancy or nursing, use of vitamins, supplements or medications known to influence chronic disease/condition, and concurrent participation in another study. The nature, purpose and risks of the study were explained to each participant before written informed consent was obtained. The study was approved by the Institutional Review Board of Arizona State University (IRB protocol # STUDY00004264) and all subjects participated in the study voluntarily, providing written informed consent prior to participation. The study was carried out at Arizona State University (ASU) from May 2016 to September 2016. This study was registered at ISRCTN and trial registration number: ISRCTN1398030.

Intervention

Subjects were given 2 mg Capsaicinoids per day (100 mg Capsimax® capsule, CAPs) or a matched placebo (microcrystalline cellulose). Supplements were supplied by OmniActive Health Technologies Ltd. India.

Equipment

The Breezing® device (an indirect mobile calorimeter), evaluates energy expenditure (EE) by detecting the rate of oxygen consumption and carbon dioxide generation in breath. It is based on a flow detection and a chemical sensing cartridge, which uses a cell-phone camera for optical detection. As reported before, Figure 1 shows the testing configuration of the current Breezing® device [15]. The device is 6.0 oz. (170 g), and 1.8 in × 2.1 in × 4.8 in (4.7 cm × 5.4 cm × 12.3 cm), and connects wirelessly to an iOS/

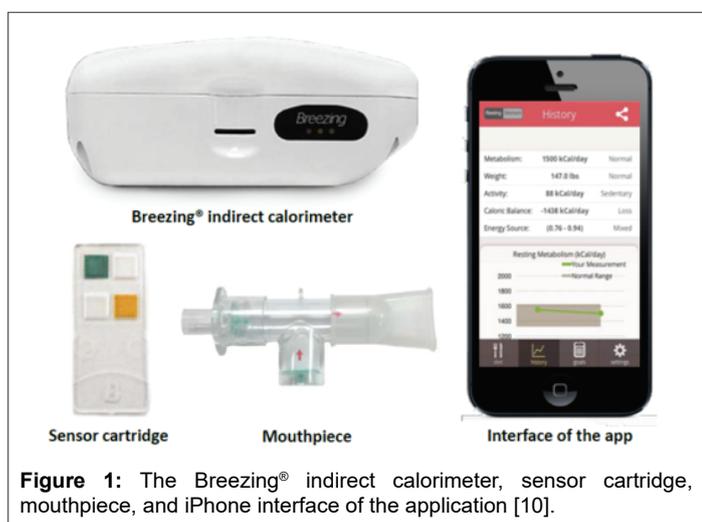
Android mobile device, via Bluetooth®. A QR code with pre-calibrated sensor information is applied on the single-use sensor cartridge, which can be scanned and recognized by the mobile application. During each measurement, participants breathed through a disposable mouthpiece connected to the Breezing® device for about 1-2 minutes until a total of 6L exhaled breath were measured by the flow meter. The data received on the mobile device is processed and displayed on the application. According to the Weir equation, RQ, VO₂ and VCO₂, energy expenditure is determined. Validation of this device has been published [10]. Accuracy of this device comparing to Quark (from Cosmed) video has been by Moscow Hospital, demonstrating 3% difference with the metabolic cart method [15]. Thus we choose Breezing device for the study because of its portability and operational easiness.

Methods

Before each test, the participants arrived without any food intake in the past 4 hours, no strenuous exercise was performed for 12 hours before the test, or no moderate exercise was performed at least 4 hours before the test. Once the resting state was assured, the participant's REE was measured. At least 2 consecutive measurements of REE were taken to assure accuracy. In addition, participants' weight, height, and fat% were assessed with Tanita bio-impedance scale, and a wall ruler. After that, participants were instructed to wear a Zephyr chest strap tracker to monitor their physiological parameters. The participants were provided with meal including a non-caloric, decaffeinated drink and certain amount of Thomas Plain Bagel and 1/3 less fat Philadelphia cream cheese based on their REE level. The ratio of calorie intake to their REE value was 0.35 for 14 participants and 0.25 for 25 participants. In the meantime, the participants were served with either a CAPs or a placebo capsule. The placebo mimicked the size and physical characteristics of the supplement pill. Each participant took the test twice: one was served with CAPs and the other one was served with placebo capsule. The study was single blind in between two tests, there was a minimum two-day wash-out period. All participants metabolic rate was measured at 1 h, 2 h, and 3 h respectively. The time to start and to finish the test was approximately 3.5h. During the blank time of the test, participants were required to perform sedentary office or bench work. The testing protocol is summarized in Figure 2a. Based on the same set of data, Figures 3b and 3c are plotted to compare the difference between two groups at same level. The REE value before the meal was considered as baseline of that participant. REE₀ denotes the baseline REE value and REE_i represents the REE value measured at 1 h, 2 h and 3 h. The data is calculated as: [(REE_i - REE₀)/REE₀]*100%.

Table 1: Baseline Characteristics.

| Details | N | Age (yr) | Height (in) | Weight (lbs) | BMI (lbs/in ²) | Bio-impedance (%) |
|---------|----|-----------------------|-----------------------|---------------------------|----------------------------|---------------------------|
| Male | 23 | 28.3 ± 5.5 (22-47) | 66.6 ± 4.7 (61-75) | 146.8 ± 32.8 (116-209) | 23.1 ± 3.9 (18.1-31.8) | 18.0 ± 7.2 (6.0-26.7) |
| Female | 17 | 28.1 ± 5.4 (23-47) | 66.4 ± 4.7 (56-69) | 145.4 ± 32.5 (99-185) | 23.0 ± 3.8 (17.2-32.8) | 18.4 ± 7.2 (13.2-44.4) |
| Total | 40 | 28.2 ± 5.3 (22-47) | 66.4 ± 4.7 (56-75) | 145.7 ± 32.8 (99-209) | 23.1 ± 3.8 (18.1-32.8) | 18.6 ± 7.2 (6.0-44.4) |



Individual participant REE

Participants were served with diet 1 in which the amount of calorie intake was 0.35 portion of their REE value. The rest of the 26 participants were served with diet 2 in which the amount of calorie intake was deducted to 0.25 portion of their REE value.

Statistical analysis

To distinguish two groups with a power of 0.95, a minimum sample size of 35 is required. In this study, we defined the sample size of 40, which is sufficient to conclude the difference. Within-treatment analyses were conducted utilizing Student's *t*-test for paired data, comparing each post-treatment time point to baseline for each treatment. The parametric between treatment analysis was performed by using analysis of covariance with the baseline value as the covariate. Treatment effects were measured at a level of statistical significance of *p*<0.05. Data are reported as Mean ± SD. The pairwise differences of least squares means of the treatments were tested with the use of Tukey-Kramer *p* value adjustments. A paired *t*-test was run on ΔREE% results shown in Figure 4. In this test, α=0.05 and the degree of freedom is 39. The level of statistical significance was set at *p*<0.05. Data are reported as Mean ± SD.

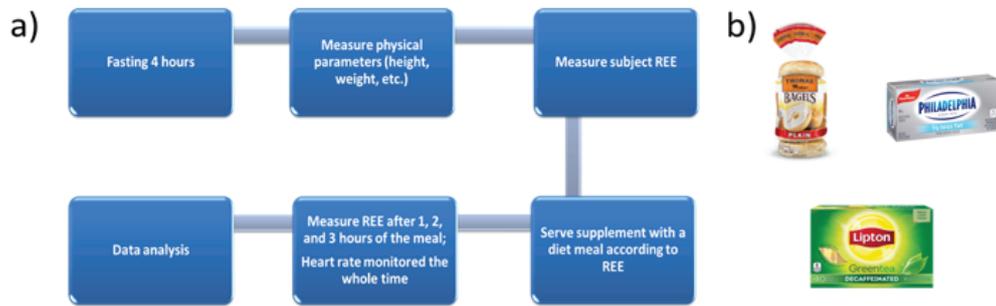


Figure 2: a) Testing protocol; b) Meal provided to participants.

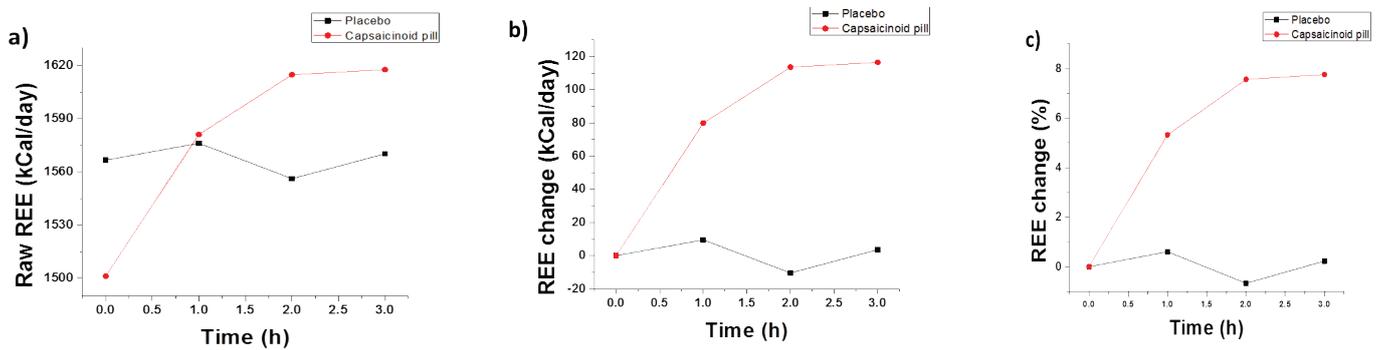


Figure 3: a) Average REE of all participants; b) Relative average REE change ($REE_t - REE_0$); c) Relative average REE change in percentage ($((REE_t - REE_0) / REE_0) * 100\%$).

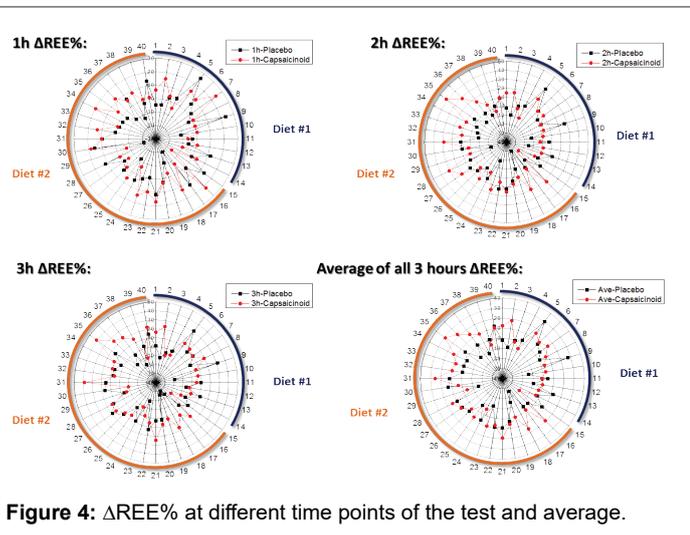


Figure 4: Δ REE% at different time points of the test and average.

Results

Total tests were performed and comparison between the CAPs and placebo capsule group was made to evaluate the enhancement of the supplement on human REE. Heart rate data was also reported for all the participants. Results are summarized in Figures 3 and 4 for all participants.

On average, the group which took CAPs capsule showed a positive REE change than placebo group. The REE level of CAPs group increased 116 Kcal/day (8%) at the end of three hours, while the placebo group shows \pm 15 Kcal/day (less than 0.7%) fluctuation over the whole test. Overall CAPs demonstrated increase in average REE.

Individual participant REE change: Metabolic rate is unique for each individual. Figure 4 shows the Δ REE% of each participant. In Figure 4, the label outside the radar plot indicates the participants' number. In Figure 4, the CAPs group is at outer cycle than placebo group. CAPs has a positive effect and demonstrated an effect on metabolic rate. An absolute area integration results are shown in Table 2. CAPs group has shown a statistically significantly positive integrated area than placebo group during the 3 hours. An increase in REE was observed in CAPs at 1 h and continue to increase at 3 h (from 505% to 1186%), indicating that CAPs enhance metabolic rate than placebo.

Heart rate profile: Participants' heart rate was monitored *via* a real-time monitoring tracker, Zephyr, in the shape of a chest band (Figure 5a). Their physiologic activity signals were recorded and reported to a PC interface every second. Figure 5b) shows the average heart rate profile of all participants. The average heart rate of CAPs group is (78.6 ± 2.72) BPM while placebo group has an average of (79.15 ± 2.88) BPM. During the test, the average heart rate in both groups increased around 10 BPM in the first 30 minutes, and then gradually recovered back to the initial heart rate. Figure 5b demonstrates that there is no significant difference in heart rate between two groups (CAPs vs Placebo). No significant difference between males and females were observed (Table 3).

The extrapolated REE change: To specifically evaluate the CAPs, we pre-rate the REE change in 24 hours after the intake of the pill. The average REE value of all participants' baseline REE was 1534 Kcal/day. Data from Figure 3c was used to pre-rate the REE change. CAPs group has shown increased REE by more than 100 Kcal/day (6%) on average than placebo group. Table 4 summarizes an example for a pre-rate REE change. We calculated pre rated REE changes in 24 h for each subject and in each treatment. It was observed that mean Pre-rated REE changes in 24 hrs for capsaicinoids were 130 Kcal/day (7.23%) and placebo was 8 kcal/day (1.17%).

Table 2: Integrated area from radar plot.

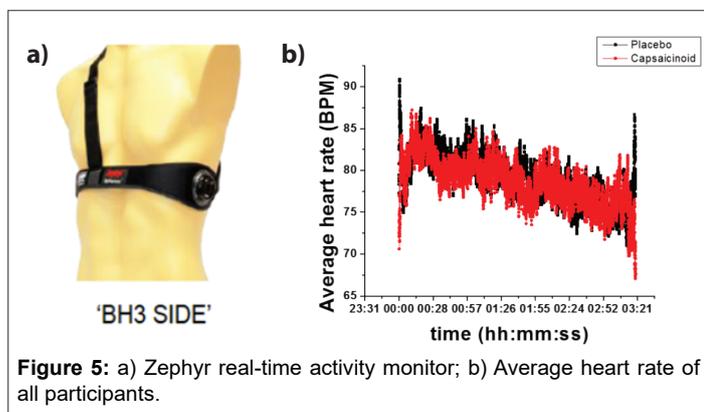
| Time | Group | Radar plot area integration (%) |
|-----------------------|---------------|---------------------------------|
| 1h | Placebo | -55 |
| | Capsaicinoids | 450 |
| 2h | Placebo | -260 |
| | Capsaicinoids | 836 |
| 3h | Placebo | -321 |
| | Capsaicinoids | 865 |
| Average of all ΔREE % | Placebo | -212 |
| | Capsaicinoids | 717 |

Table 3: ΔREE % comparison by treatments (capsaicinoids vs placebo) and by gender.

| Paired t-test between Capsaicinoids and Placebo group | | | | |
|---|-------|-------|-------|---------|
| ΔREE % | 1h | 2h | 3h | Average |
| p value | 0.115 | 0.006 | 0.023 | 0.012 |
| Significance | No | Yes | Yes | Yes |
| T-test between female and male group | | | | |
| ΔREE % | 1h | 2h | 3h | Average |
| p value | 0.48 | 0.62 | 0.72 | 0.78 |
| Significance | No | No | No | No |

Table 4: Pre-rated REE change.

| Pre-rated REE changes in 24hrs Group | 1h | 2h | 3h | Average |
|--------------------------------------|---------------------|----------------------|----------------------|----------------------|
| Placebo | 26 kCal/day (1.27%) | 18 kCal/day (0.52%) | 19 kCal/day (1.72%) | 8 kCal/day (1.17%) |
| Capsaicinoids | 73 kCal/day (4.79%) | 130 kCal/day (8.48%) | 129 kCal/day (8.43%) | 111 kCal/day (7.23%) |



subgroups and assists in increasing subject compliance. Very limited studies are available on indirect calorimetry and stand alone supplements in healthy populations. Some of the studies are focused on combination products and energy expenditure. Rudelle et al. [21] recently reported that consumption of a beverage containing mainly green tea catechins (700 mg), caffeine (100 mg), and calcium (211 mg), when consumed three times per day for three days, increased 24-hour energy expenditure (EE) by 4.6% in healthy male and female subjects. Twenty-four-hour energy expenditure (EE) and 24-hour fat oxidation were lower in women than in men ($p < 0.0001$ and $p < 0.015$, respectively). Although there were no treatment or treatment/gender effects on substrate oxidation, treatment increased 24-hour EE by 106 ± 31 kcal/24 hours ($p = 0.002$), equivalent to 4.7 ± 1.6 kcal/h (day; $p = 0.005$) and 3.3 ± 1.5 kcal/h (night; $p = 0.04$). No significant differences were observed in hemodynamic parameters [21]. Overall combination products with thermogenic ingredients had an effect on energy expenditure. In this study, ΔREE% was significant over placebo at different time points. This may be due to the thermogenic effect from capsaicinoids. In another study, Dulloo et al. [22] reported a mixture of caffeine and green tea reported a 4% increase in 24-hour energy expenditure after the consumption. current study, CAPs group has shown an increased REE more than 100 Kcal/day (6%) on average than placebo. The current data was consistent with other studies that have found the portable analyzer of REE produce significantly higher measurements of energy expenditure than the indirect calorimeter [23,24]. In a systematic review reported by Hipskind et al. [25], on hand-held calorimeters search resulted in a total of 54 published articles; 23 of these specifically are about hand-held calorimeter devices. The results suggest hand-held calorimeters were similar to those obtained from metabolic cart studies. Hand-held calorimeters are more accurate than predictive equations based on gender, age and ethnicity for determining resting metabolic rate and are therefore a viable alternative for clinical evaluation. Previous and current data suggest that the breezing hand-held indirect calorimeter has potential application in clinical evaluations and epidemiology or field research in which typical metabolic carts or other standard methods are not practical.

Total energy expenditure (TEE) consists of three major components: basal metabolic rate (BMR), thermogenic effect of food, and the effect of physical activity or exercise. In this study, a thermogenic supplement CAPs had an effect on EE over placebo. Thermogenic effect of food refers to the heat the body generates as food is digested. There are limitations to the fact that it is an open label acute single administered cross over placebo controlled study and the positive effect of CAPs is subject dependent. CAPs treated subjects showed a positive effect, and there was a statistical significant difference with $p < 0.05$ overall. As it is a personal metabolic rate tracking profile it would be necessary to determine the personal effect of the supplement in each individual over a period of time for further recommendations to maintain weight management.

Discussion

We evaluated the accuracy of a portable and mobile indirect calorimeter [Breezing®] device measuring EE in free-living adults. In this study, predictive equations are used to estimate resting energy expenditure (REE). Equations were included when based on weight, height, age, and/or gender. Our findings suggest the device is reasonable and easy to access to track EE daily. Accurate self-monitoring in the free-living environment may provide helpful feedback that increases self-awareness of sedentary life style, overweight and obesity an important element for positive decision making and lifestyle changes [18-20]. These types of studies, however, need to be performed in larger and more diverse sample populations (e.g. children, older adults, obese persons, and athletes) at different age groups in health and disease to determine whether the Breezing® device is accurate across various population

Conclusion

In conclusion, although the data are preliminary, the Breezing device provides valid REE estimates in healthy adults. These results suggest a significant increase in REE (6.07%) to CAPs compared with placebo. The extrapolated REE changes in 24 hrs for capsaicinoids were 130 kcal/day and placebo was 8 kcal/day. No changes in heart rate and adverse events were observed. These findings indicate that capsaicinoids are thermogenic and may increase resting REE. Further long term clinical studies are required to explore the metabolic tracker and use of supplements in nutritional studies for weight management.

Acknowledgement

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Conflict of Interest

None of the authors have any conflicts to disclose. Authors YD and FC are researchers at ASU and declare no relationship. EF is patent inventor of Breezing equipment and received funding support from OmniActive Health Technologies Ltd. India. VJ is an employee of OmniActive Health Technologies Inc.

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