

# Aframomum melegueta Seed Extract with Standardized Content of 6-Paradol Reduces Visceral Fat and Enhances Energy Expenditure in Overweight Adults – A Randomized Double-Blind, Placebo-Controlled Clinical Study

Heggar Venkataramana Sudeep<sup>1</sup>, Khanna Aman<sup>2</sup>, Thomas V Jestin<sup>3</sup>, Kodimule Shyamprasad<sup>1</sup>

<sup>1</sup>Department of Biomedical Research (R&D), Vidya Herbs Pvt Ltd, Bangalore, Karnataka, 560 105, India; <sup>2</sup>Aman Hospital and Research Center, Vadodara, Gujarat, 390021, India; <sup>3</sup>Leads Clinical Research and Bio Services Private Ltd, Bangalore, India

Correspondence: Heggar Venkataramana Sudeep, Research Scientist, R&D Center for Excellence, Vidya Herbs Pvt Ltd, No. 14/A, KIADB, Jigani Industrial Area, Anekal Taluk, Bangalore, Karnataka, 560 105, India, Tel +91 80-42094158, Email [research@vidyaherbs.com](mailto:research@vidyaherbs.com); [sudeepkashyap.82@gmail.com](mailto:sudeepkashyap.82@gmail.com);

**Purpose:** *Aframomum melegueta* (grains of paradise) seeds have been demonstrated to possess thermogenic potential. However, it is necessary to validate the functional attributes of *A. melegueta* seed extract in human subjects.

**Methods:** In a double-blind, placebo-controlled clinical trial design, we have examined the thermogenic effects of a standardized *A. melegueta* seed extract (AferFit). A total of 70 overweight male and female subjects (BMI  $\geq 25.0$  to  $\leq 30.0$  kg/m<sup>2</sup>) aged 20–50 years were enrolled and administered with either 250 mg of AferFit or placebo in capsule form twice daily for 12 weeks. The primary efficacy endpoints included energy expenditure (indirect calorimetry), body composition (dual-energy X-ray absorptiometry (DEXA)) and fat distribution (computed tomography (CT scan)), analyzed at baseline and after 12 weeks of treatment. The effect of intervention on the quality of life was examined using SF-12 questionnaire.

**Results:** Consumption of AferFit significantly increased the energy expenditure ( $p < 0.01$ ), visceral fat area ( $p < 0.001$ ) and visceral to subcutaneous fat ratio ( $p < 0.01$ ) compared to placebo group. Consequently, there was significant body weight loss and reduction in BMI of subjects in AferFit group compared to placebo ( $p < 0.01$ ). The safety evaluation showed that biochemical and hematological parameters were in the normal range. Supplementation of AferFit was well tolerated during the study and no adverse effects were observed.

**Conclusion:** Overall, this study validates the health benefits of *A. melegueta* seed extract as fat burner and recommends its use as a functional ingredient to improve the quality of life and general health.

**Keywords:** grains of paradise, fat burner, 6-paradol, visceral fat

## Introduction

In the modern world, obesity is a global health concern with alarming consequences such as cardiovascular diseases, diabetes, and cancer.<sup>1–3</sup> Of the various approaches to manage obesity, stimulation of thermogenic program has gained significant attention.<sup>4</sup> Natural thermogenic supplements are publicly available in the market to promote weight loss alongside the diet restrictions and exercise.<sup>5,6</sup> These supplements include combination of herbal extracts that can enhance the resting metabolic rate and reduce body fat.<sup>7</sup> In this regard, the physiological functions of several herbal constituents and preparations have been demonstrated by researchers. Green tea extract rich with polyphenols has been reported to induce thermogenesis via adiponectin signaling.<sup>8</sup> Recently, Caffeine was demonstrated to enhance the physical activity-driven caloric cost in rats.<sup>9</sup> Recently Katada et al<sup>10</sup> reported that a 2-week consumption of catechins with caffeine

markedly increased the energy expenditure in middle-aged human subjects. Use of such thermogenic agents is a promising strategy to mitigate obesity and associated metabolic diseases.

*Aframomum melegueta* (Fam. Zingiberaceae) is a perennial herb originated from Western parts of Africa.<sup>11</sup> *A. melegueta* is commonly known as grains of paradise or *melegueta* pepper or guinea grains. The seeds of the plant are used in food and ethnomedicinal preparations. The plant is reported to contain phenolic compounds such as paradols, shogaols and gingerols.<sup>12</sup> These bioactive vanilloid compounds possess various biological functions including antioxidant, anti-inflammatory, and anti-proliferative activities.<sup>13–15</sup> Further, there are reports on the usefulness of these compounds against metabolic diseases. In a recent study from Hattori et al,<sup>16</sup> the synthetic vanilloid compounds were investigated for anti-obesity effects in male mice. A 2-week oral administration of 6-paradol significantly reduced the visceral and subcutaneous fat depots, while the effect was not observed with 6-gingerol and 6-shogaol.

The thermogenic effects of *A. melegueta* seed extract and its active compound 6-paradol have been studied previously.<sup>17,18</sup> Earlier, we found that oral administration of AfperFit, a standardized *A. melegueta* seed extract, significantly induced beige adipocytes in high-fat diet-induced obese mice via activation of browning genes.<sup>19</sup> To further validate the therapeutic claims of AfperFit, we have investigated its weight loss effects in healthy overweight humans.

## Materials and Methods

### Ethical Approval and Consent

The Institutional Ethics Committee of Aman Hospital and Research Center, Vadodara, India, approved the study protocol and informed consent form (AHRC/IEC/030/2018). This clinical study was registered in Clinical Trials Registry – India (CTRI/2019/03/017956 dated 07/03/2019).

### Investigational Product

AfperFit is a proprietary herbal extract from *Aframomum melegueta* seeds formulated in powder form to contain not less than 2% 6-paradol. The pungent active constituents of AfperFit viz., 6-paradol ([Supplementary Figure 1](#)), 6-gingerol and 6-shogaol ([Supplementary Figure 2](#)) were analyzed by HPLC ([Supplementary File](#); Characterization of 6-paradol, 6-gingerol and 6-shogaol in AfperFit). Each 250 mg capsule contained 5 mg of 6-paradol. The placebo capsules had similar appearance and color. The investigational product was stored at 15–35 °C protected from light and moisture at the clinical study site.

### Subjects

Seventy overweight (BMI  $\geq 25.0$  to  $\leq 30.0$  kg/m<sup>2</sup>) male and female subjects aged 20–50 years were enrolled in the trial. Before enrolment, the volunteers were explained the study protocol. All the subjects provided the informed consent. Subject enrolment was initiated on May 13, 2019 and ended on September 27, 2019.

Subjects suffering from chronic health conditions (eg, diabetes, hypertension, chronic renal failure, heart, and liver disease), fasting blood glucose above normal limits, history of chronic metabolic disease, psychiatric illness, drug abuse, smoking, addiction to alcohol, endocrine abnormalities, and history of surgery were excluded from the study.

### Study Design

The clinical study to investigate the safety and efficacy of AfperFit was conducted in compliance with ICH-GCP (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use –Good Clinical Practice) guidelines and Helsinki Declaration Standards. This clinical study adheres to the CONSORT guidelines ([Supplementary File](#)).

A randomized, double-blind, placebo-controlled, two arm, single centered clinical study was conducted in healthy overweight male and female human subjects. The study was conducted at Aman Hospital and Research Center, Vadodara, Gujarat, India. A population size of 70 subjects were randomized to two treatment arms: AfperFit and placebo on 1:1 ratio (n = 35 in each group). The subjects received oral doses of 250 mg capsules twice daily (before breakfast and

dinner) for 84 days (12 weeks). The study treatment details are provided in [Supplementary Table 1](#). After the baseline/screening visit, two visits were scheduled at the study site during the intervention period at an interval of 6 weeks.

## Sample Size

A sample size of 70 subjects (35 per group) was considered sufficient to detect a clinically important difference between groups with 80% power and a 5% level of significance. Considering an estimated potential dropout rate of 12%, the sample size was finalized as 70 (35 per group). The details are provided in the [Supplementary File](#).

## Randomization

The interventions were masked and assigned a code for each. The subjects were randomized using block randomization with a block size of 4. The random allocation sequence was generated by the biostatistician and the subjects enrolled by the investigator. The investigator and the subjects were blinded by the interventions.

## Study Outcomes

The primary endpoint analyses included determination of energy expenditure, body composition, and fat distribution at baseline and at the end of study (after 12 weeks of treatment).

Energy expenditure was measured by indirect calorimetry (FitMate WM, Cosmed, USA). The subjects were fasted for 8 h and examined early in the morning. The measurement was performed with subjects in supine position for 10–15 min, in a ventilated room void of external noise. The device was calibrated before each measurement.

Body composition analysis at baseline and after 12 weeks of treatment was performed using dual-energy X-ray absorptiometry (DEXA) (Lunar iDXA, GE Healthcare, India).

The fat distribution was examined by computed tomography (CT scan). The CT scan was performed with subjects in the supine position. One slice was collected at fourth and fifth lumbar vertebrae (L4-L5). Before segmentation of body fat, the background noise and unnecessary regions were removed. Body fat was then detected with pixels between –190 and –30 Hounsfield units (HU). Segmentation mask was generated from the binary images to differentiate the visceral and subcutaneous fat. The images were processed using ImageJ software.

The secondary endpoints included safety assessment (serum lipid profile, blood biochemical parameters and complete blood count). The 12-term Short Form Survey (SF-12) questionnaire was used to assess the quality of life.

## Statistical Analysis

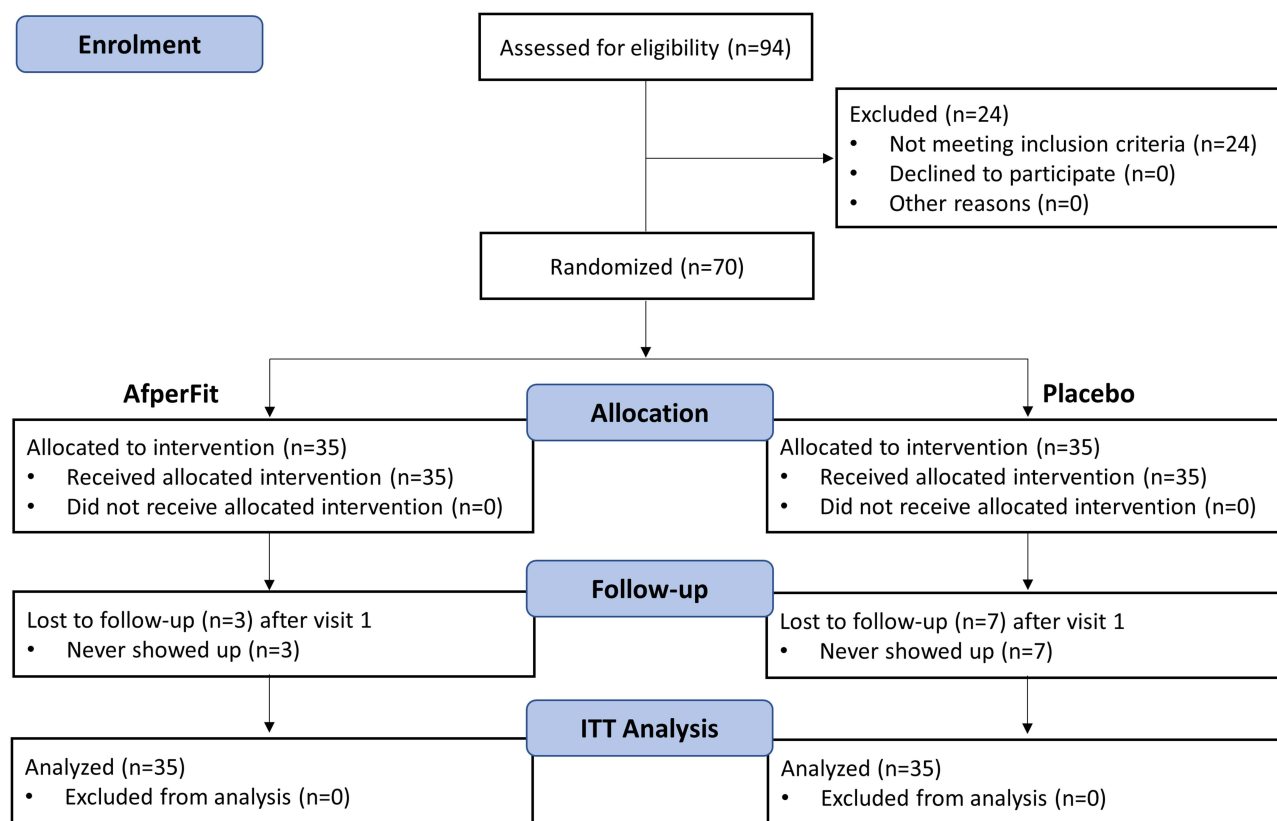
All the data were analyzed for normality of distribution. The normally distributed data were analyzed by paired sample *t*-test (within the group) and independent *t* test (between the groups). Skewed data were analyzed by non-parametric tests: Mann–Whitney test for two independent groups and Wilcoxon test for paired data (within the group). The covariates were analyzed using ranked ANCOVA. The values were presented as mean ± SD. Data were considered statistically significant at  $p < 0.05$ . In the case of dropouts, the missing subject data for ITT analysis were handled by imputation analysis (last observation carried forward).

## Results

A total of 94 human volunteers were screened for inclusion in the trial. Seventy subjects meeting the inclusion criteria were enrolled in the study. Of the 70 subjects randomized to two treatment groups ( $n = 35$  in each group), 60 subjects completed the study. There were 10 dropouts in the study (reason: lost to follow up). The intention-to-treat (ITT) analysis was used to assess the outcome of the study. The participant flow through the study is presented in [Figure 1](#). The demographic characteristics of subjects between the groups were not significantly different ([Table 1](#)). The efficacy and safety analysis were performed using ITT population.

## Efficacy Analysis

[Table 2](#) shows the effect of AfperFit on energy expenditure in overweight subjects. The energy expenditure was measured using indirect calorimetry at baseline and after 12 weeks of treatment. AfperFit group showed 18.55% increase



**Figure 1** Study participant flow diagram in accordance with CONSORT 2010. Adapted from Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. PLoS Med. 2010;7(3): e1000251. Copyright: © 2010 Schulz et al. Creative Commons Attribution License.<sup>20</sup>

in the mean energy expenditure from baseline at the end of study ( $p < 0.001$ ). The placebo group showed an insignificant increase of 3.32% in the energy expenditure (Figure 2A). The change in energy expenditure was significantly higher in the AfperFit group as compared to placebo group ( $p < 0.01$ ) (Figure 2B).

The body composition parameters were determined using DEXA analysis (Table 3) (Figure 3). A significant reduction in body fat (%) was noticed in both the groups ( $p < 0.01$ ). The body fat reduction from baseline to the end of treatment was slightly superior in AfperFit group. However, the data were not significant between the groups. There was a significant decrease in body fat mass observed in both AfperFit ( $p < 0.001$ ) and placebo groups ( $p < 0.01$ ) at the end of study. The mean change in fat mass was higher in AfperFit group than the placebo group.

**Table 1** Demographic Characteristics of Subjects

Parameter	AfperFit (N=35)	Placebo (N=35)	p value <sup>#</sup>
Age (Years)	36.57±9.22	36.05±7.97	0.800
Weight (kg)	72.78±9.54	69.17±7.27	0.079
Height (cm)	161.47±9.81	158.43±8.55	0.171
BMI (kg/m <sup>2</sup> )	27.84±1.73	27.54±1.73	0.467
Waist to hip ratio	0.89±0.06	0.87±0.07	0.153

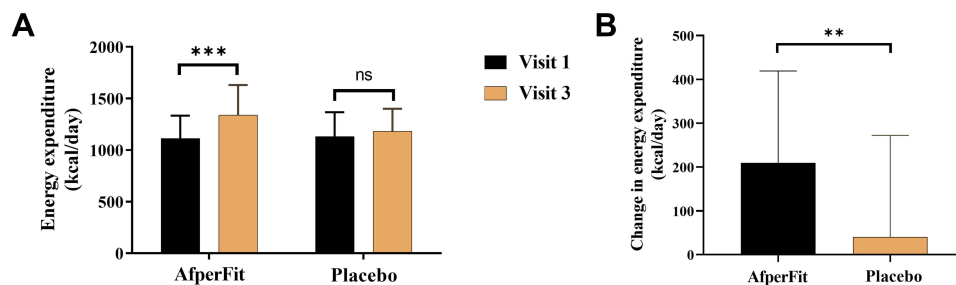
**Notes:** Data were analyzed by independent sample t test. <sup>#</sup> $p < 0.05$  was considered as statistically significant. BMI: body mass index.

**Table 2** Effect of AfperFit on Whole-Body Energy Expenditure (Kcal/Day)

Parameter	AfperFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
Visit 1	1128.94±232.69	752.00	1087.00	1710.00	1212.43±349.24	741.00	1099.00	2409.00	0.418 <sup>‡</sup>
Visit 3	1338.31±287.89	928.00	1260.00	2070.00	1252.69±331.14	848.00	1184.00	2409.00	0.109 <sup>‡</sup>
Change (Visit 3-Visit 1)	209.37±209.74	-196.00	161.00	717.00	-2.13±4.20	-533.00	13.00	664.00	0.004 <sup>***</sup>
p value	<0.001 <sup>###</sup>				0.124 <sup>#</sup>				

Notes: <sup>#</sup>Wilcoxon signed-rank test (Visit 1 vs Visit 3); <sup>‡</sup>Mann-Whitney U-test (between the groups). \*\*p<0.01; \*\*\*p<0.001.

Abbreviations: N, No. of subjects; SD, standard deviation.



**Figure 2** Energy expenditure in AfperFit and placebo groups at baseline and 12 weeks was determined by indirect calorimetry (A). Changes in energy expenditure between the groups was recorded (B). Values are presented as mean ± SD (n=35 in each group). The data were analysed using paired t test within the group and independent t test between the groups. \*\*p<0.01 and \*\*\*p<0.001.

Abbreviations: ns, not significant; SD, standard deviation

Interestingly, a decreasing trend was observed in lean mass of AfperFit group from baseline to the end of treatment ( $p<0.01$ ). On the contrary, placebo group showed an increase in lean mass ( $p<0.05$ ). The change in lean mass of AfperFit group was significant compared to the placebo ( $p<0.001$ ).

Another aspect of efficacy analysis was to examine the effect of AfperFit on the body fat distribution. Table 4 shows the summary of fat distribution among the subjects. After 12-week supplementation of AfperFit, there was a noticeable reduction ( $p<0.01$ ) in the visceral fat area, whereas the same was increased to a significant extent in the placebo group ( $p<0.05$ ). The mean change from baseline to the end of treatment in AfperFit group was significant ( $p<0.001$ ) as compared to placebo. The subcutaneous fat area was reduced in either groups and the mean change between the groups was not significant. The visceral-to-subcutaneous fat ratio was reduced to a significant extent in the AfperFit group

**Table 3** Summary of Changes in Body Composition Parameters of Subjects (DEXA Analysis)

Parameter	AfperFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Body fat (%)</b>									
Visit 1	43.52±6.83	31.20	43.60	56.50	44.46±7.54	30.60	46.80	57.50	0.581 <sup>‡</sup>
Visit 3	40.68±8.44	26.40	38.70	58.10	42.32±7.92	26.70	43.70	54.30	0.488 <sup>‡</sup>
Change (Visit 3-Visit 1)	-2.84±4.75	-12.20	-0.6	7.8	-2.13±4.20	-12.40	0.00	2.80	0.417 <sup>‡</sup>
p value	0.007 <sup>###</sup>				0.022 <sup>##</sup>				

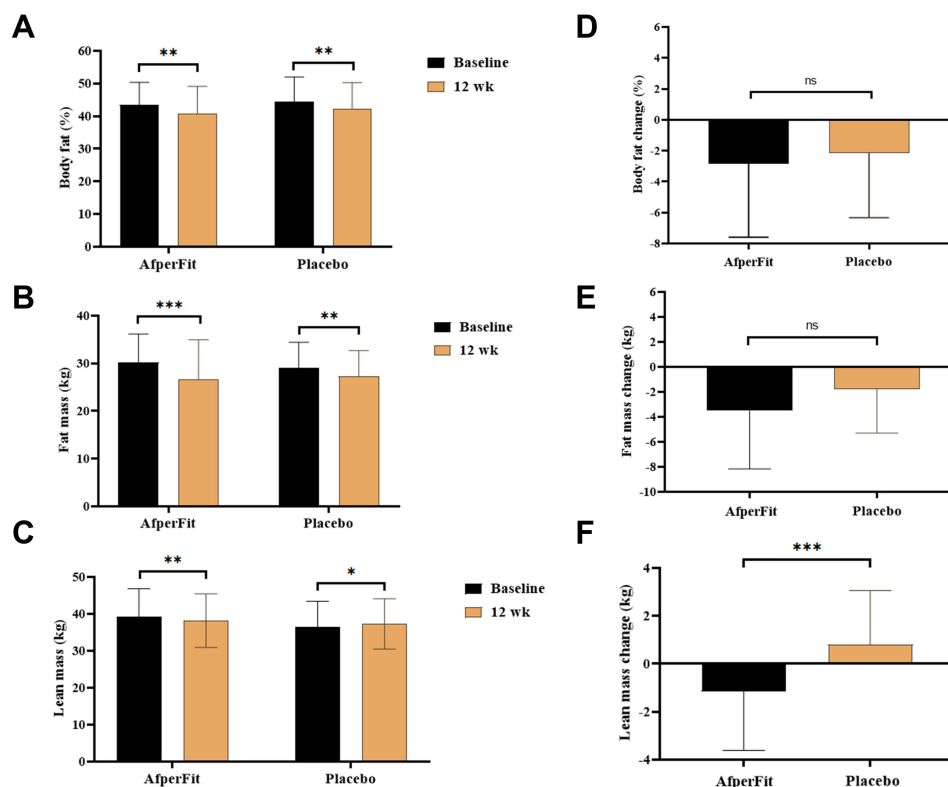
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Table 3 (Continued).

Parameter	AferFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Fat mass (kg)</b>									
Visit 1	30.18±6.00	19.73	29.20	45.29	29.06±5.35	18.22	29.96	39.05	0.7511 <sup>‡</sup>
Visit 3	26.67±8.27	13.95	25.82	45.31	27.27±5.40	15.07	27.32	36.56	0.4067 <sup>‡</sup>
Change (Visit 3-Visit 1)	-3.51±4.66	-14.63	-0.94	3.36	-1.79±3.51	-11.38	-0.22	2.41	0.1337 <sup>‡</sup>
p value	<0.001 <sup>#***</sup>				0.017 <sup>#*</sup>				
<b>Lean mass (kg)</b>									
Visit 1	39.33±7.50	28.55	37.99	50.97	36.51±6.89	25.01	34.63	50.20	0.113 <sup>‡</sup>
Visit 3	38.19±7.26	25.91	37.51	51.40	37.32±6.82	26.13	35.57	49.85	0.591 <sup>‡</sup>
Change (Visit 3-Visit 1)	-1.14±2.47	-9.56	-0.65	3.23	0.81±2.25	-2.41	0.00	7.99	0.002 <sup>‡</sup>
p value	0.007 <sup>#**</sup>				0.099 <sup>#</sup>				

Notes: <sup>#</sup>Wilcoxon signed-rank test (Visit 3 vs Visit 1); <sup>‡</sup>Mann-Whitney U-test (between the groups). \*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

Abbreviations: N, No. of subjects; SD, standard deviation.



**Figure 3** Summary of changes in body composition parameters (DEXA analysis). (A) Body fat %, (B) fat mass and (C) lean mass measured at baseline and 12 weeks of treatment. (D-F) Comparison of changes in these parameters from baseline to the end of study. Values are presented as mean  $\pm$  SD (n=35 in each group). The data were analysed using paired t test within the group and independent t test between the groups. \*p<0.05, \*\*p<0.01 and \*\*\*p<0.001.

Abbreviations: SD, Standard deviation; DEXA, Dual-energy X-ray absorptiometry.

( $p < 0.05$ ). On the contrary, the ratio was increased from baseline to the end of study in placebo group ( $p < 0.05$ ). The reduction in the visceral-to-subcutaneous fat ratio from baseline was significant in AferFit compared to placebo group ( $p < 0.01$ ) (Figure 4).

The mean body weight and BMI changes were recorded (Table 5). The DEXA analysis revealed that the AferFit group showed significant reduction in the body weight and BMI from baseline to the end of treatment ( $p < 0.001$ ). The mean changes in body weight and BMI from baseline were significant in AferFit group as compared to placebo ( $p < 0.01$ ) (Figure 5).

The efficacy parameters were not significantly changed with respect to age and gender as covariates (Table 6).

The effect of AferFit administration on general health was determined using quality of life questionnaire (SF-12). The objective assessment included total SF-12 score, physical component score (PCS-12) and mental component score (MCS-12). SF-12 total score in AferFit group was significantly increased from baseline ( $29.40 \pm 1.58$ ) to the end of study ( $31.69 \pm 2.10$ ) ( $p < 0.001$ ). The change in the total score of AferFit group ( $-2.29 \pm 1.76$ ) was found to be significant ( $p < 0.001$ ) as compared to placebo ( $0.20 \pm 2.70$ ). Similar trend was observed in MCS-12 score. However, there was no significant change in the PCS-12 score of the treatment groups (Table 7).

To summarise the efficacy measures, a 12-week oral supplementation of 500 mg/day AferFit could exert thermogenic effect by significantly increasing the energy expenditure and reducing the body fat % and visceral fat. There was an obvious reduction in the body weight and BMI of the subjects in AferFit group.

## Safety Analysis

No serious adverse events were recorded during the study. Liver function and renal function parameters were evaluated at baseline and the end of the study. The parameters were found to be within the normal range throughout the study. No clinically significant differences in the biochemical parameters were observed between the groups at the end of study (Table 8).

Serum lipid parameters were found to be within normal levels throughout the study period. A significant ( $p < 0.05$ ) reduction from baseline in total cholesterol, LDL cholesterol, and LDL: HDL ratio was observed in AferFit group. No clinically significant difference was found between the AferFit and placebo groups (Table 9). Table 10 shows the haematological assessment of subjects. In the AferFit group, there were marginal variations in the parameters except for

**Table 4** Effect of AferFit on Body Fat Distribution of Subjects

Parameter	AferFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Visceral fat area (cm<sup>2</sup>)</b>									
Visit 1	71.42±31.12	24.35	63.7	169.61	66.42±33.85	14.58	57.32	162.31	0.366 <sup>‡</sup>
Visit 3	54.83±28.42	13.62	55.38	121.89	86.25±59.00	14.58	75.05	316.57	0.011 <sup>‡</sup>
Change (Visit 3-Visit 1)	-16.59±28.14	-79.16	-13.17	40.34	19.83±50.54	-50.66	11.13	230.2	<0.001 <sup>‡***</sup>
p value	0.002 <sup>##**</sup>				0.026 <sup>##*</sup>				
<b>Subcutaneous fat area (cm<sup>2</sup>)</b>									
Visit 1	703.51±83.12	528.71	690.71	913.16	753.97±81.70	598.91	754.32	970.66	0.012 <sup>‡**</sup>
Visit 3	663.70±115.38	364.10	674.66	881.88	705.99±103.22	370.60	722.39	861.38	0.067 <sup>‡</sup>
Change (Visit 3-Visit 1)	-39.81±110.87	-341.30	-4.23	87.04	-47.98±110.38	-285.3	-4.63	169.20	0.499 <sup>‡</sup>
p value	0.194 <sup>##</sup>				0.020 <sup>##*</sup>				

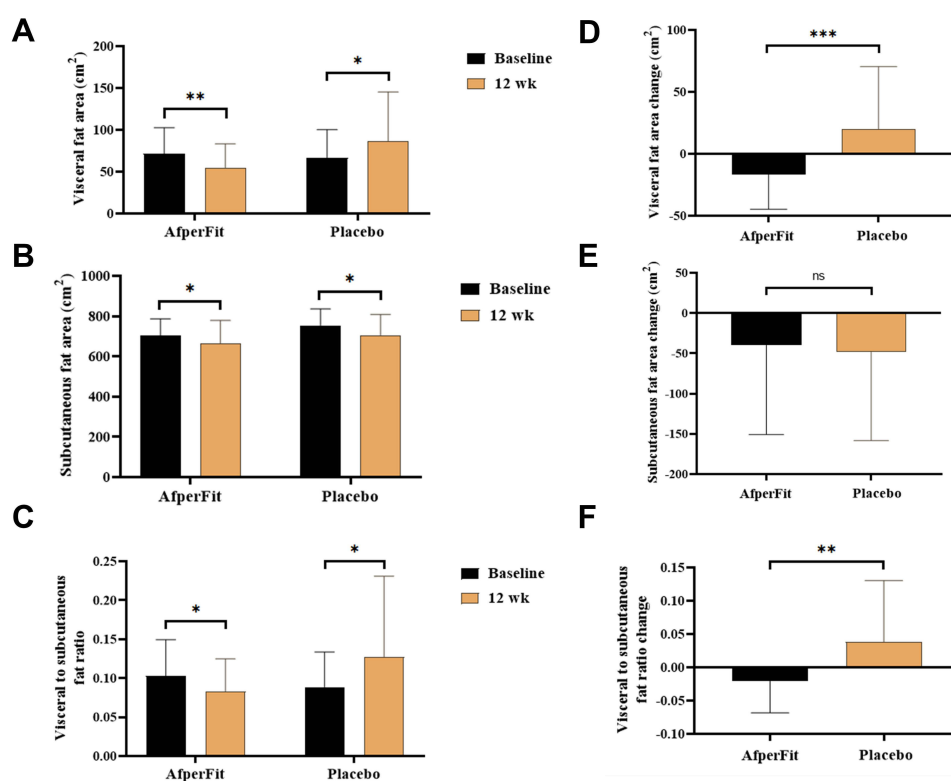
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Table 4 (Continued).

Parameter	AferFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Visceral/subcutaneous fat ratio</b>									
Visit 1	0.10±0.05	0.042	0.092	0.210	0.09±0.04	0.022	0.077	0.206	0.178 <sup>‡</sup>
Visit 3	0.08±0.04	0.023	0.080	0.216	0.13±0.10	0.022	0.108	0.608	0.021 <sup>‡*</sup>
Change (Visit 3-Visit 1)	-0.020±0.05	-0.140	-0.016	0.098	0.039±0.09	-0.056	0.016	0.498	<0.001 <sup>‡***</sup>
p value	<0.001 <sup>#***</sup>				<0.001 <sup>#***</sup>				

Notes: <sup>#</sup>Wilcoxon signed-rank test (Visit 1 vs Visit 3); <sup>‡</sup>Mann-Whitney U-test (between the groups). \*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

Abbreviations: N, No. of subjects; SD, standard deviation.



**Figure 4** Summary of fat distribution assessment (Computed tomography analysis). (A) Visceral fat area, (B) subcutaneous fat area and (C) visceral-to-subcutaneous fat ratio measured at baseline and 12 weeks of treatment. (D-F) Comparison of changes in these parameters from baseline to the end of study. Values are presented as mean ± SD (n=35 in each group). The data were analysed using paired t test within the group and independent t test between the groups. \*p<0.05, \*\*p<0.01 and \*\*\*p<0.001. Abbreviation: SD, Standard deviation.

significant increase in the hemoglobin, mean cell volume (MCV) and mean cell haemoglobin (MCH) and a decrease in platelet count ( $p<0.05$ ).

## Discussion

The present study investigated the weight loss effects of AferFit, a standardized *A. melegueta* extract containing not less than 2% 6-paradol, in overweight subjects of either sex. A 12-week ingestion of AferFit at 500 mg/day significantly increased the energy expenditure compared to the placebo group. Further, the CT analysis of subjects revealed that AferFit reduced the visceral fat in subjects to a significant extent compared to placebo. On the contrary, the change in

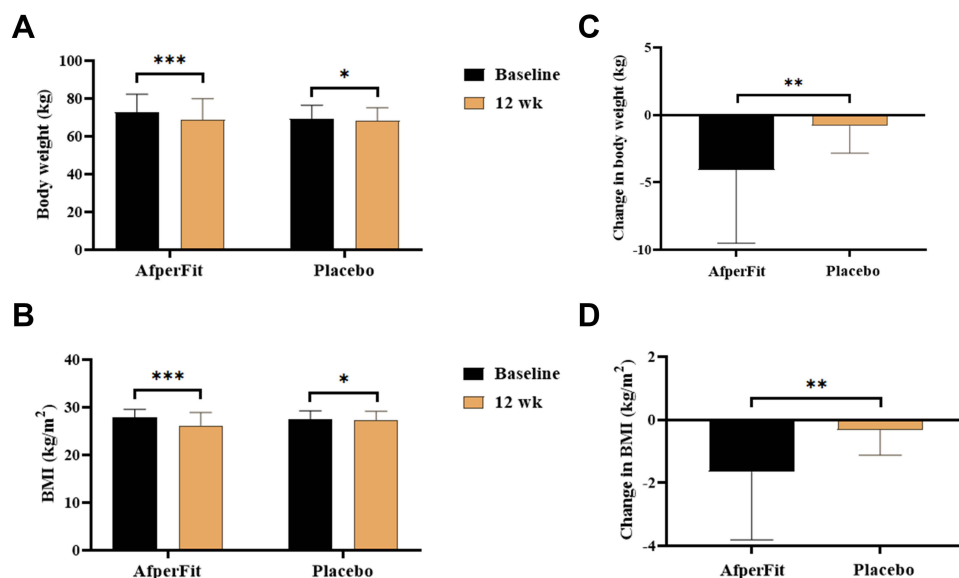


**Table 5** Effect of AfperFit on Body Weight and BMI

Parameter	AfperFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Body weight (kg)</b>									
Visit 1	72.78±9.54	54.40	73.00	91.50	69.17±7.27	55.00	68.00	89.00	0.152 <sup>‡</sup>
Visit 3	68.71±11.28	45.90	72.00	87.00	68.36±6.85	52.60	68.20	82.00	0.702 <sup>‡</sup>
Change (Visit 3-Visit 1)	-4.07±5.45	-21.10	-1.60	1.00	-0.81±2.03	-7.00	-0.40	4.20	0.009 <sup>***</sup>
#p-value	<0.001 <sup>##***</sup>				<0.001 <sup>##***</sup>				
<b>BMI (kg/m<sup>2</sup>)</b>									
Visit 1	27.84±1.73	25.10	28.10	31.10	27.54±1.73	25.00	27.40	29.80	0.394 <sup>‡</sup>
Visit 3	26.19±2.71	20.10	26.70	30.80	27.22±1.93	23.90	27.30	31.70	0.184 <sup>‡</sup>
Change (Visit 3-Visit 1)	-1.65±2.16	-8.00	-0.80	0.30	-0.32±0.81	-2.30	-0.10	1.90	0.003 <sup>***</sup>
#p-value	<0.001 <sup>##***</sup>				0.035 <sup>##*</sup>				

**Notes:** <sup>#</sup>Wilcoxon signed-rank test (Visit 1 vs Visit 3); <sup>‡</sup>Mann-Whitney U-test (between the groups). \*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

**Abbreviations:** N, No. of subjects; SD, standard deviation.



**Figure 5** Changes in body weight and BMI. The mean body weight and BMI of AfperFit (A) and placebo (B) groups were recorded at baseline and 12 weeks of treatment. (C&D) Comparison of changes in these parameters from baseline to the end of study. Values are presented as mean ± SD (n=35 in each group). The data were analysed using paired t test within the group and independent t test between the groups. \*p<0.05, \*\*p<0.01 and \*\*\*p<0.001.

**Abbreviations:** SD, Standard deviation; BMI, Body mass index.

subcutaneous fat was insignificant between AfperFit and placebo groups. The preference of AfperFit to the visceral fat is interesting, because visceral adipocytes are associated more with the risk of cardiovascular diseases in humans.<sup>21,22</sup> Also, in humans, the browning genes are predominantly expressed in the visceral fat than the subcutaneous fat.<sup>23</sup> These findings are agreeing with the previous study from Sugita et al<sup>24</sup> who reported that daily consumption of 30 mg *A. melegueta* extract for 4 weeks soared the energy expenditure and reduced visceral fat accumulation. Further, the present clinical study data are in line with our previous findings that AfperFit mediated browning of visceral fat via increased expression of UCP1, PPAR $\gamma$  and PGC-1 $\alpha$  in high fat diet-fed mice.<sup>19</sup>

**Table 6** Results of Rank Analysis of Covariance (ANCOVA) (with Age and Gender as Covariates) of Changes in Efficacy Parameters from Baseline

Parameter	Cofactor	p value	F value
Visceral fat area	Treatment	<0.001***	17.089
	Gender	0.694	0.156
	Age	0.109	2.636
Subcutaneous fat area	Treatment	0.503	0.453
	Gender	0.431	0.627
	Age	0.881	0.023
Energy expenditure	Treatment	0.002**	10.060
	Gender	0.046*	4.133
	Age	0.399	0.718
Body mass index	Treatment	0.003**	9.670
	Gender	0.600	0.278
	Age	0.688	0.163
Body fat %	Treatment	0.419	0.661
	Gender	0.509	0.441
	Age	0.765	0.090
Fat mass	Treatment	0.138	2.257
	Gender	0.512	0.435
	Age	0.951	0.004
Lean mass	Treatment	0.002**	10.575
	Gender	0.391	0.745
	Age	0.765	0.090

Notes:  $p < 0.05$  were considered statistically significant; \* $p < 0.05$ , \*\* $p < 0.01$  and \*\*\* $p < 0.001$ .

**Table 7** Summary of Short-Form Health Survey (SF-12) Questionnaire

Visit	AfperFit (N=35)	Placebo (N=35)	p-value Between Groups
<b>Total score</b>			
Baseline (Visit 1)	29.40±1.58	30.03±2.12	0.164 <sup>‡</sup>
End of study (Visit 3)	31.69±2.10	29.83±2.67	0.002 <sup>‡*</sup>
Change	2.29±1.76	-0.20±2.70	0.001 <sup>‡**</sup>
p-value (Visit 1 vs Visit 3)	<0.001 <sup>‡**</sup>	0.664 <sup>#</sup>	
<b>Physical component score (PCS-12)</b>			
Baseline (Visit 1)	12.60±1.50	12.77±1.31	0.612 <sup>‡</sup>
End of study (Visit 3)	12.57±1.42	12.89±1.43	0.360 <sup>‡</sup>

(Continued)

Table 7 (Continued).

Visit	AferFit (N=35)	Placebo (N=35)	p-value Between Groups
Change	-0.03±1.10	0.11±1.53	0.655 <sup>‡</sup>
p-value (Visit 1 vs Visit 3)	0.879 <sup>#</sup>	0.661 <sup>#</sup>	
<b>Mental component score (MCS-12)</b>			
Baseline (Visit 1)	16.80±1.73	17.26±1.62	0.257 <sup>‡</sup>
End of study (Visit 3)	19.11±1.41	16.94±2.03	<0.001 <sup>‡***</sup>
Change	2.31±1.98	-0.31±2.26	<0.001 <sup>‡***</sup>
p-value (Visit 1 vs Visit 3)	<0.001 <sup>#***</sup>	0.416 <sup>#</sup>	

Notes: Data are mean±SD. Change = Visit 3 – Visit 1. <sup>#</sup>Paired t-test; <sup>‡</sup>Independent t-test. \*p<0.01; \*\*p<0.001.

Abbreviations: N, No. of subjects.

Table 8 Safety Analysis – Serum Biochemical Parameters

Parameter	AferFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Aspartate aminotransferase (U/L)</b>									
Visit 1	25.63±4.95	16.30	26.10	36.20	26.60±4.89	18.40	26.50	37.30	0.449 <sup>‡</sup>
Visit 3	24.14±4.52	15.30	24.20	32.80	24.70±4.82	16.40	25.10	34.10	0.609 <sup>‡</sup>
Change (Visit 3-Visit 1)	-1.49±4.33	-11.20	-0.50	8.30	-1.90±4.67	-12.80	-1.20	7.20	0.728 <sup>‡</sup>
p value	0.091 <sup>#</sup>				0.032 <sup>#*</sup>				
<b>Alanine aminotransferase (U/L)</b>									
Visit 1	24.11±5.94	16.60	22.10	38.90	25.50±5.74	19.20	24.10	40.20	0.160 <sup>‡</sup>
Visit 3	26.21±5.35	16.60	26.60	36.20	26.56±5.78	18.60	25.20	36.90	0.902 <sup>‡</sup>
Change (Visit 3-Visit 1)	2.10±4.31	-5.20	2.10	13.30	1.05±4.75	-13.45	0.00	13.40	0.445 <sup>‡</sup>
p value	0.009 <sup>#***</sup>				0.127 <sup>#</sup>				
<b>Alkaline phosphatase (U/L)</b>									
Visit 1	89.01±17.60	54.70	89.10	120.30	91.22±16.05	49.50	94.20	115.20	0.442 <sup>‡</sup>
Visit 3	88.66±16.46	60.30	88.90	122.40	90.23±15.56	50.40	92.30	115.20	0.463 <sup>‡</sup>
Change (Visit 3-Visit 1)	-0.35±11.59	-49.10	1.80	27.20	-0.99±7.10	-22.00	0.00	13.20	0.353 <sup>‡</sup>
p value	0.647 <sup>#</sup>				0.608 <sup>#</sup>				
<b>Serum creatinine (mg/dL)</b>									
Visit 1	0.95±0.11	0.75	0.97	1.26	0.98±0.13	0.70	0.98	1.26	0.413 <sup>‡</sup>
Visit 3	0.96±0.10	0.72	0.98	1.14	1.01±0.13	0.82	0.98	1.30	0.244 <sup>‡</sup>
Change (Visit 3-Visit 1)	0.01±0.09	-0.25	0.04	0.17	0.03±0.09	-0.16	0.02	0.22	0.883 <sup>‡</sup>
p value	0.210 <sup>#</sup>				0.099 <sup>#</sup>				

Notes: <sup>#</sup>Wilcoxon signed-rank test (Visit 1 vs Visit 3); <sup>‡</sup>Mann-Whitney U-test (between the groups). \*p<0.05; \*\*p<0.01.

Abbreviations: N, No. of subjects; SD, standard deviation.

**Table 9** Safety Analysis – Serum Lipid Profile

Parameter	AferFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Total cholesterol (mg/dL)</b>									
Visit 1	197.84±40.63	121.90	191.60	324.50	188.43±41.07	102.4	185.2	317.7	0.431 <sup>‡</sup>
Visit 3	191.01±39.81	120.30	182.40	319.90	185.59±38.18	104.8	185.2	317.7	0.672 <sup>‡</sup>
Change (Visit 3-Visit 1)	-6.83±18.68	-107.6	-3.20	10.70	-2.83±11.53	-27.40	-2.40	47.40	0.733 <sup>‡</sup>
p value	<0.001 <sup>#***</sup>				0.005 <sup>#**</sup>				
<b>Triglycerides (mg/dL)</b>									
Visit 1	138.59±28.03	74.80	138.70	192.30	136.17±33.18	69.80	138.5	204.4	0.792 <sup>‡</sup>
Visit 3	138.93±27.85	74.00	137.20	190.60	133.50±30.38	70.20	136.5	204.4	0.496 <sup>‡</sup>
Change (Visit 3-Visit 1)	0.34±14.84	-14.00	-5.80	-1.70	2.66±11.68	-46.30	-1.80	35.60	0.906 <sup>‡</sup>
p value	0.011 <sup>#*</sup>				0.024 <sup>#**</sup>				
<b>LDL-cholesterol (mg/dL)</b>									
Visit 1	128.14±38.06	64.84	122.00	247.80	122.02±43.64	45.84	117.20	258.50	0.565 <sup>‡</sup>
Visit 3	120.91±37.75	62.90	116.60	244.40	116.65±34.39	47.96	116.60	237.00	0.869 <sup>‡</sup>
Change (Visit 3-Visit 1)	-7.22±18.85	-107.60	-2.96	11.74	-5.37±23.18	-125.10	-2.96	45.28	0.593 <sup>‡</sup>
p value	<0.001 <sup>#***</sup>				0.011 <sup>#*</sup>				
<b>HDL-cholesterol (mg/dL)</b>									
Visit 1	41.95±1.66	39.50	41.60	47.20	42.01±1.94	39.80	41.60	48.40	0.925 <sup>‡</sup>
Visit 3	42.61±2.23	39.90	42.00	52.60	42.32±1.36	39.80	42.10	46.20	0.720 <sup>‡</sup>
Change (Visit 3-Visit 1)	0.66±2.05	-4.00	0.50	10.50	0.66±2.05	-5.00	0.30	5.10	0.433 <sup>‡</sup>
p value	0.003 <sup>#***</sup>				0.028 <sup>#**</sup>				

Notes: <sup>#</sup>Wilcoxon signed-rank test (Visit 1 vs Visit 3); <sup>‡</sup>Mann-Whitney U-test (between the groups). \*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

Abbreviations: N, No. of subjects; SD, Standard Deviation.

In the present study, body composition was measured using the validated DEXA analysis. There was a significant reduction in the body fat % and fat mass of subjects treated with both AferFit and placebo. However, the changes were more pronounced in the active treatment group.

The lean mass was significantly reduced in the AferFit-treated subjects. Several other studies on the antiobesity effects of dietary supplements have shown 14–50% reduction in lean body mass.<sup>25–27</sup> Based on the observed trend, it can be presumed that AferFit could not offset the loss of lean mass. A moderate to intense physical activity contributes to retain lean mass in a weight loss program.<sup>28</sup> Hence, supplementation of AferFit with augmented dietary manifestations and exercise could help preserve lean body mass.

Interestingly, none of the efficacy endpoint parameters were influenced by the age and gender of the subjects.

The quality of life was assessed using validated multipurpose SF-12 questionnaire. AferFit treated subjects showed a significant increase in mental component score and the total score compared to the placebo group. These results clearly suggest that AferFit has a positive impact on the general health. Furthermore, there was no abnormal change observed in the biochemical and hematological parameters. The observed changes in hemoglobin, MCV, MCH and platelet count of AferFit group were not significant compared to placebo and can be considered incidental.

**Table 10** Safety Analysis – Haematological Assessment

Parameter	AferFit (N=35)				Placebo (N=35)				p value (Between Groups)
	Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max	
<b>Total leukocyte count (cm<sup>3</sup>)</b>									
Visit 1	7374.29±1520.52	4200	6800	9900	7822.86±1473.91	5200	7700	9800	0.171 <sup>‡</sup>
Visit 3	7491.43±1415.75	5100	7400	10,200	7554.29±1430.83	5200	7400	10,400	0.981 <sup>‡</sup>
Change (Visit 3-Visit 1)	-117.14±1038.52	-2200	300	2600	268.57±1049.59	-3000	0	1400	0.165 <sup>‡</sup>
p value	0.477 <sup>#</sup>				0.186 <sup>#</sup>				
<b>Red blood cell count (million/cm<sup>3</sup>)</b>									
Visit 1	5.09±0.49	4.31	4.91	6.29	4.99±0.32	4.35	4.99	5.66	0.724 <sup>‡</sup>
Visit 3	4.92±0.59	4.01	4.89	7.99	4.93±0.27	4.49	4.92	5.66	0.509 <sup>‡</sup>
Change (Visit 3-Visit 1)	0.18±0.66	-1.28	0.00	2.63	0.06±0.21	-0.60	-0.01	0.40	0.444 <sup>‡</sup>
p value	0.032 <sup>#</sup>				0.088 <sup>#</sup>				
<b>Hemoglobin (g/dL)</b>									
Visit 1	13.51±0.68	12.00	13.80	14.60	13.33±0.56	12.00	13.50	14.20	0.116 <sup>‡</sup>
Visit 3	13.58±0.51	12.40	13.50	14.00	13.28±0.42	12.40	13.40	14.10	0.251 <sup>‡</sup>
Change (Visit 3-Visit 1)	0.13±0.39	-0.90	-0.20	0.60	0.05±0.40	-0.80	0.00	0.70	0.413 <sup>‡</sup>
p value	0.062 <sup>#</sup>				0.373 <sup>#</sup>				
<b>Platelet count (cm<sup>3</sup>)</b>									
Visit 1	300,228.60 ±54,702.45	199,000	298,000	407,000	283,857.10 ±43,095.75	208,000	268,000	365,000	0.247 <sup>‡</sup>
Visit 3	282,714.30 ±46,625.27	209,000	289,000	382,000	279,685.70 ±52,932.13	208,000	284,000	369,000	0.851 <sup>‡</sup>
Change (Visit 3-Visit 1)	17,514.29±48,992.42	-113,000	-23,000	114,000	4171.43±41,437.75	-71,000	0	105,000	0.261 <sup>‡</sup>
p value	0.019 <sup>#</sup>				0.374 <sup>#</sup>				

Notes: <sup>#</sup>Wilcoxon signed-rank test (Visit 1 vs Visit 3); <sup>‡</sup>Mann-Whitney U-test (between the groups).

Abbreviations: N, No. of subjects; SD, standard deviation.

AferFit has a standardized content of 6-paradol along with the presence of other pungent compounds such as 6-gingerol and 6-shogaol. These compounds have been reported to possess different biological activities including antihyperglycemic and lipid lowering effects.<sup>29,30</sup> The presence of these compounds could be attributed to the observed thermogenic effects of AferFit. Iwami et al<sup>17</sup> have previously demonstrated the thermogenic potential of *A. melegueta* seed extract and particularly 6-paradol in rats. The authors reported the mechanism of action as activation of brown adipose tissue (BAT) through the stimulation of sympathetic nerve activity. In another study, 6-paradol was shown to have profound anti-obesity effects in high fat diet-fed mice via activation of brown adipose tissue.<sup>18</sup> These reports further support the outcome of the present study.

The limitation of the present study is that we have not measured the impact of AferFit on substrate oxidation alongside resting energy expenditure. Secondly, the study had considerable drop-outs. The strength of the study is that the primary outcome measures were obtained using instrumental analyses, which guaranteed the data accuracy and reliability.

## Conclusion

In conclusion, the present study demonstrated that daily intake of 500 mg of AfperFit for 12 weeks significantly increased the energy expenditure while reducing the body fat and visceral fat. The study outcome strongly supports the weight loss potentials of AfperFit.

## Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Disclosure

The authors Heggara Venkataramana Sudeep and Kodimule Shyamprasad are employed by Vidya Herbs Pvt Ltd., Khanna Aman is employed by Aman Hospital and Research Center, Vadodara, India. Thomas V Jestin is employed by Leads Clinical Research and Bio services Private Ltd., Bangalore, India. The authors report no other conflicts of interest in this work.

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