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Research Article

EFFICACY AND TOLERABILITY OF A NOVEL FORMULATION FOR WEIGHT MANAGEMENT IN OBESE SUBJECTS: A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, CLINICAL STUDY

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ABSTRACT

Obesity is a complex interplay between environmental and genetic factors, is also associated with significant morbidity and mortality. The primary objective of the present study was to evaluate the efficacy and safety of Calebin A (standardized extract of *Curcuma caesia*) in the management of weight in obese or overweight individuals. A randomized, mono-centric, double-blind, placebo-controlled, clinical study was conducted by administering Calebin A (standardized extract of *Curcuma caesia*) capsules (25 mg, one capsule twice a day) and indistinguishable placebo capsules as daily supplements to 40 overweight and obese subjects for 90 days. The study participants were divided in 1:1 ratio to receive either Calebin A (standardized extract of *Curcuma caesia*) (n = 20) or placebo (n = 20).

Efficacy was assessed by measuring body weight, body mass index, leptin, adiponectin levels, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and Hs-CRP. Safety was assessed by evaluating safety parameters (vital signs and laboratory investigations) and monitoring adverse events.

After 90 days, significant reduction in body weight (P< 0.0001) and body mass index (P < 0.0001) were observed in the Calebin A (standardized extract of *Curcuma caesia*) group compared with placebo. Additionally, significant change in serum biomarkers was observed between Calebin A (standardized extract of *Curcuma caesia*) and placebo groups from baseline to final visits. Adverse events were mild and were unrelated to the investigational products. Supplementation with Calebin A (standardized extract of *Curcuma caesia*) resulted in significant decrease in weight loss than placebo over 90 days. It was safe and well tolerated by all subjects.

KEYWORDS: *Curcuma caesia*, Leptin, Adiponectin, Body weight, Body mass index.

INTRODUCTION

Obesity arises from an imbalance in energy consumption over energy expenditure.[1] At the cellular level, this imbalance results in an increase in the size and number of mature adipocytes.[2–4]

In 2008, the world health organization estimated that about 1.5 billion adults (aged 20 and above) were overweight with nearly 500 million of these individuals classified as obese.[5]

The study - titled 'Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the global burden of disease study 2013' - used data collected by international bodies and organisations in various countries like India over three decades. The US topped the list with 13 per cent of the obese people worldwide in 2013, while China and India together accounted for 15 per cent of the world's obese population, with 46 million and 30 million obese people, respectively. According to the study, number of overweight and obese people globally increased from 857 million in 1980 to 2.1 billion in 2013. This is one-third of the world's population.

Overweight in adults is categorised as those with Body Mass Index of 25 kg/m^2 to 30 kg/m^2 and obesity as those with Body Mass Index of more than 30 kg/m^2. As per the study, in 2010, overweight and obesity were estimated to cause 3 to 4 million deaths, 3.9 per cent of years of life lost and 3.8 per cent of disability adjusted life-years worldwide.

With lifestyle disorders forcing more and more people to reel under excess body weight, even relatively younger people are developing joint disorders and knee pain. Excessive weight is associated with a series of health problems, including blood pressure, diabetes and cardiovascular ailments. Yet another problem is that obesity puts people at an increased risk of developing osteoarthritis. Experts say the prevalence of obesity is greater in urban areas, and more women are affected than men.[6]

Current treatments for obesity include pharmacotherapy, bariatric surgery and lifestyle modification.[7] Pharmacotherapy involves the use of anti-obesity drugs such as phentermine and orlistat.[8, 9]

The preferred treatment modality for weight loss is dieting and physical exercise. Due to busy schedules and sedentary lifestyle follow-up the first two methods never seems to be practiced in a regular manner. On the other hand, weight loss surgery runs out of the option considering the cost involved. There is a gradual shift towards an increased use of drugs. Drugs are pharmacological agents that reduce or control weight.

These drugs alter one of the fundamental processes of the human body. Due to potential side effects, it is recommended that anti-obesity drugs only be prescribed for obesity where it is hoped that the benefits of the treatment outweigh its risk.[10]

The use of allopathic and pharmacological drugs has become a popular means to overcome excess weight gain.[11] While these drugs generally are effective, severe adverse toxicities may limit their overall usefulness.[12, 13] A nutritional based intervention is being hailed as an inexpensive alternative to aid weight loss, and weight management.[14] Natural plant based phytoextracts with enriched phytonutrients in the form of supplements are being extensively utilized due to their effectiveness in managing many chronic disorders. They are cost-effective, and exert less to no toxic side-effects in comparison with many chemically synthesized drugs.[15] Accordingly, recent preliminary reports suggested that herbs with a long history of use and other natural substances less likely to produce severe toxicity might be effective in reducing appetite and promoting significant weight loss are encouraging.[16]

Curcuma caesia Roxb (black turmeric) is a perennial herb with bluish black rhizomes and it is famous for its medicinal properties.

Calebin A, being a ferulate ester lacks the characteristic feature of curcuminoid i.e., 1, 3-diketonic structure.[17]

A study conducted to investigate the chemo preventive effects of dietary *Curcuma caesia* (Calebin A) on differentiation of 3T3-L1 adipocytes and high-fat diet (HFD) induced obesity and hepatic steatosis. Potential mechanisms contributing to these effects were also elucidated. Calebin A effectively and dose dependently suppressed accumulation of lipid droplets in adipocytes through the suppression of adipogenic specific factor peroxisome proliferator-activated receptor (PPAR) γ and fatty acid synthesis and activated acetyl-CoA carboxylase. Dietary Calebin A effectively decreased weight gain and relative perigonadal, retroperitoneal and mesenteric fat weight in HFD-fed mice.[18]

Based on the above study, Sami Labs Limited conducted a repeated dose (90 day) study to assess the oral toxicity, reproductive/developmental toxicity and mutagenic potential of *Curcuma caesia* (Calebin A).

Curcuma caesia (Calebin A) was orally administered to groups of 10 male and/or 10female Wistar rats each, assigned to three dose levels (20, 50 and 100 mg/kg/body weight)once daily for 90 consecutive days. None of the animals in any of the treatment/control groups exhibited any abnormal clinical signs/behavioural changes, reproductive as well as developmental parameters, or gross and microscopic changes in both male and female rats.[19]

We hypothesized that *Curcuma caesia* (Calebin A) would help in weight management of obese or overweight individuals.

MATERIALS &METHODS

Study Product Description

Calebin A (standardized extract of *Curcuma caesia*) was encapsulated in size zero hard Gelatin capsules with excipients. Placebo capsules with equivalent weight of micro-crystalline cellulose. No differences in colour, taste, texture or packaging were detectable between the two products. Capsules were sealed in identically-appearing, high-density polyethylene bottles with desiccant.

Table 1: Composition detail of *Curcuma caesia* capsule

#	Ingredients	Label Claim	Overages	mg per capsule
1	Calebin A (standardized extract of *Curcuma caesia*)	25 mg	5%	26.25
2	Micro-crystalline cellulose			368.75
3	Magnesium stearate			5.0
'00' Golden Yellow/ Golden Yellow HG capsules				

Ethics Approval

The study protocol and related documents were reviewed by Institutional Ethics Committee of Life Care Hospital, Bangalore, prior to study initiation. The aforesaid Ethics Committee was registered under CDSCO as per the Gazette Notification Number F.28-10/45-H(1), dated 21 DEC 1945 and last amended vide notification number G.S.R. 76(E) dated 08 FEB 2012.

Informed Consent

Written and oral information about the study in a language understandable by the subject was provided to all subjects. Each subject was informed by the investigator, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and documented the informed consent process in the subject's chart. Prior to entry into the study or initiation of any study-related procedures, the subject read, signed and dated the Institutional Ethics Committee approved informed consent form. Sufficient time was provided for each subject to decide whether to participate in the study and all the questions and clarifications regarding the study were clarified by the investigator. The person executing the consent also signed and dated the final consent form page.

Participants

A total of forty subjects were enrolled in the study. Eligibility requirements included male and female patient's age between 20 and 65 years and body mass index (BMI) between 25 to 40 Kg/m^2. Subjects willing to come for regular follow-up visits and able to give written informed consent were recruited.

Subjects were excluded if they were not otherwise healthy, were pregnant or nursing and had in previous six months taken over the counter weight loss agents, centrally acting appetite suppressants or prior surgical therapy for obesity. Patients with pathophysiologic/ genetic syndromes associated with obesity, evidence of malignancy, poorly controlled Diabetes mellitus or hypertension or clinical evidence of heart failure were excluded. Alcoholics and/or drug abusers as well as patients with history of HIV and other viral infections or history of hypersensitivity to any herbal extract or dietary supplement. Patients were not included if they have concurrent serious hepatic disorder (AST/ALT, total bilirubin, ALP > 2 times upper normal limit) or renal disorders (serum creatinine> 1.2 mg/dL) or severe pulmonary dysfunction or patients on prolonged (> 6 weeks) medication with corticosteroids, antidepressants, anticholinergics, etc.

Trial Design

The clinical trial was a randomized, double-blind, placebo-controlled, clinical study to evaluate the efficacy and safety of Calebin A (standardized extract of *Curcuma caesia*).This trial study was performed at Life Care Hospital, Bangalore. At baseline evaluation, subjects were provided active or placebo capsules, compliance cards and dates for follow-up evaluations.

All subjects filled out a questionnaire providing details regarding medical history and the diet at baseline as well as all follow-up evaluations at Day 30, Day 60 and Day 90. At baseline and subsequent follow-up visits, subjects were assessed for body weight, body mass index and waist and hip circumference, serum biomarkers (leptin, adiponectin, ESR and Hs-CRP), lipid profile and clinical photographs. Safety was assessed by determining changes in vitals, blood chemistries, liver enzymes, adverse events.

Supplementation

All participants in the experimental group received Calebin A (standardized extract of *Curcuma caesia*) supplementation over a 90 day period. The participants in the placebo group received capsules of similar size and colour. They were given identical instructions on dosage of study supplement to be followed. Active and placebo were supplied in opaque white plastic bottles containing a known number of capsules. Subjects were directed to take one capsule at least 30 minutes after meal, twice a day (2 capsules per day) and to return unused pills, which were counted to determine adherence. The administration of treatment and placebo was blinded for both the participants and the investigator. At the end of the study, a representative of Sami Labs Limited revealed the supplement code to the researchers. There were no side effects reported by the participants as a result of the supplementation.

Randomisation & Allocation Concealment

The randomisation sequence was prepared by an independent statistician, independent of the sponsoring organization and not involved in conduct or reporting of the study. Alphabetical code was generated for both the active and placebo to improve the blindness of the study and concealment of allocations. Computer generated random allocation software (version 2.0) was used for the allocation of concealment. Block randomization (only one block) was followed wherein the subjects were randomized to receive either active or placebo. The randomization codes were kept strictly confidential and were accessible only to authorized persons on an emergency basis as per the Sponsor standard operating procedures until the time of unblinding.

Blinding

The study was double blinded wherein neither the Investigator nor the trial participants knew whether they would receive Calebin A (standardized extract of *Curcuma caesia*) or placebo. The investigational products were provided in pre labelled containers to avoid bias.

Statistical Analysis

Statistical Analysis Software (SAS) of version 9.2 software was used for data analysis. Paired 't' test, Analysis of Covariance (ANCOVA) and Wilcoxon signed rank sum test were used for appropriate data set variables to reach the best possible statistical conclusion between *Curcuma caesia* (Calebin A) and Placebo groups. The baseline descriptors were summarized as mean and standard deviations for continuous variables and as frequencies and percentages for categorical variables. *p*-values less than 0.05 were considered to be statistically significant for between-group comparisons. All comparisons reported are between the placebo and the *Curcuma caesia* (Calebin A) groups at each specified time point.

Results

Demographic Characteristics: Demographic characteristics of the study subjects are summarized in Table 2.

Reduction in body weight and BMI

The present study evaluated the efficacy of *Curcuma caesia* (Calebin A) on weight loss, lipid profiles, serum adiponectin level in comparison with placebo group. *Curcuma caesia* (Calebin A) supplementation for 90 days resulted in statistically significant reduction in body weight and BMI ($p< 0.0001$) (Table 2).

Changes in Waist and Hip Circumferences

The reduction in waist circumferences, after supplementation with placebo or *Curcuma caesia* (Calebin A), is summarized in Table 2.

Supplementation with the *Curcuma caesia* (Calebin A) resulted in net decrease ($p<0.0001$) in waist circumferences at the end of the study. It was also found that the net impact of the *Curcuma caesia* (Calebin A) on waist circumference was statistically significant compared with placebo.

Improvement in Serum Adiponectin

Curcuma caesia (Calebin A) supplementation resulted in ($p <0.01$) increase in serum adiponectin concentration compared to the placebo group at the end of the study (Figure 2).This observation suggests the reduced fat store in *Curcuma caesia* (Calebin A) supplemented subjects. Interestingly, it is also suggestive that *Curcuma caesia* (Calebin A) might be a potential candidate for improving cardiovascular health in obese humans.

Modulation of Serum Markers and Lipid Profile

Figures 3 and 4 illustrate that *Curcuma caesia* (Calebin A) supplementation for 90 days resulted in a significant decrease of leptin levels and Hs-CRP ($p< 0.01$) compared with placebo.

It was noted that *Curcuma caesia* (Calebin A) supplementation significantly decreased total cholesterol, LDL cholesterol and triglyceride levels and increased HDL cholesterol levels ($p< 0.0001$) (Table 4).

Adverse Events

No major adverse events were reported during this study. Minor adverse events such as gastrointestinal irritation, leg pain were noted at various evaluation time points. However, these events were not likely to be associated with Calebin A (standardized extract of *Curcuma caesia*) supplementation.

Safety Evaluations

Vital signs such as Blood Pressure, Respiratory Rate, Pulse Rate and any abnormal lab parameters were considered for safety evaluations. No clinically significant changes were recorded for descriptive physical examination in both the groups (Calebin A (standardized extract of *Curcuma caesia*) and placebo). Further, no clinically significant abnormal lab values were identified and no statistically significant changes in the vitals were observed from the baseline to final visits. There were no serious adverse events noticed in this study.

Dropouts

Five subjects (two from the Calebin A (standardized extract of *Curcuma caesia*) group and three from the placebo group) were dropped from the study and were lost to follow-up (Figure 1). The results attributed to the dropouts were excluded from all statistical analysis.

DISCUSSION

A total of 41 subjects were screened and 40 were enrolled into the study and randomized into *Curcuma caesia* (Calebin A) and placebo groups in 1:1 ratio for a period of 90 days, as one capsule twice a day, at least 30 minutes after meals reported significant decrease in weight towards end of the study in *Curcuma caesia* (Calebin A) receiving group when compared to placebo receiving group. The clinical efficacy parameters of anthropometric, lipid profile and serum biomarkers have suggested that the group receiving *Curcuma caesia* (Calebin A) is showing a good trend in the reduction of weight.

Lipid parameters for patients receiving *Curcuma caesia* (Calebin A) showed significant decrease in total cholesterol, triglycerides, LDL cholesterol and a significant increase in HDL cholesterol. Serum biomarkers analysis (adiponectin, leptin, hs-CRP, Erythrocyte Sedimentation Rate) showed that *Curcuma caesia* (Calebin A) was significantly effective when compared to placebo.

There were no major study product related adverse events. Minor adverse effects reported in the study were all unrelated to the investigational products. With no abnormal laboratory values, changes in the vital signs, and with no statistical difference ($P>0.05$) between the treatment groups, *Curcuma caesia* (Calebin A) as dietary supplement could be confirmed showing significant efficacy for overweight/obesity.

This study provides preliminary evidence on weight loss benefits of *Curcuma caesia* that are in line with other studies conducted elsewhere across the world.

CONCLUSION

Obesity and overweight are serious health problems that have reached epidemic proportions. Weight problems can have a negative impact on quality of life and, in the case of obesity, can even lead to a significant reduction in life expectancy. Due to safety concerns and side effects of many prescription weight loss drugs, herbal remedies are becoming increasingly popular as alternatives to prescription medications for weight loss.

The present study demonstrated significant beneficial effects on body weight, anthropometry, lipid profile, biomarkers, lipid parameters, biomarkers. No study product related adverse events were reported.

In summary, the results of current clinical study reveal that *Curcuma caesia* (Calebin A) may be an effective and safe nutraceutical in reducing weight in overweight/ obese adults. Thus, we conclude that larger multi-site trials are needed to elucidate the potential mechanisms of action and role of *Curcuma caesia* (Calebin A) in management of overweight/obesity.

Registration

The trial was registered on the Clinical Trial Registry of India with the registration number CTRI/2016/01/006487on 07/Jan/2016.

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Figure 1: Flow chart of the clinical study design

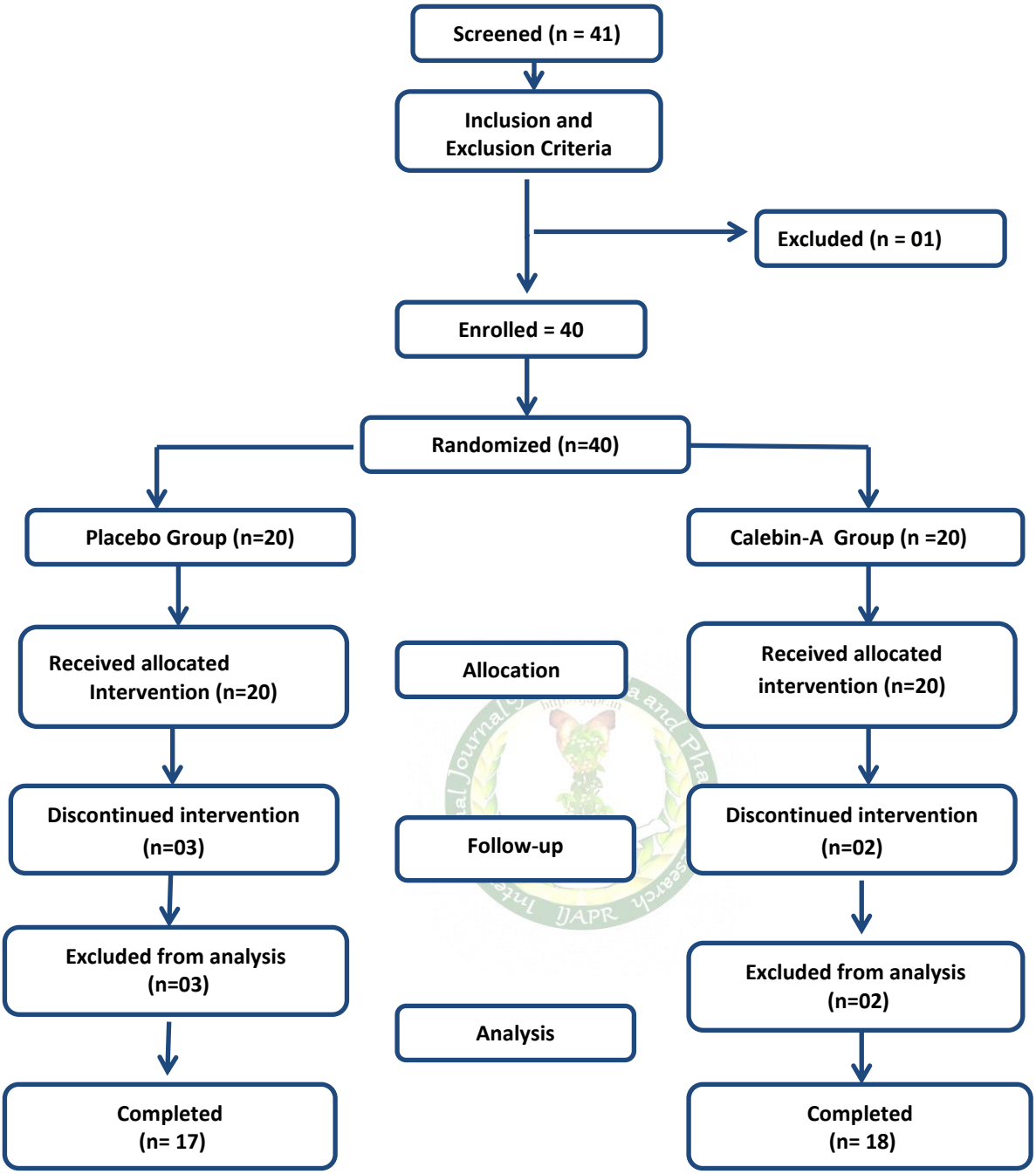

Table 2: Demographic data and baseline characteristics of the study subjects

Characteristics	Placebo (n=17)	*Curcuma Caesia* (Calebin A) (n=18)
Number of males	05	05
Number of females	12	13
Age (years)	36.94 (8.33)	35.11 (8.83)
Weight (kg's)	76.9 (11.08)	90.13 (14.75)
Height (meters)	1.56 (0.07)	1.60 (0.1)
Body Mass Index (kg/m^2)	31.30 (3.31)	34.93 (4.53)

Values are expressed as mean (standard deviation)

Table 3: Changes in Physical Parameters from baseline to Day 90 in the Placebo and in *Curcuma caesia* (Calebin A) supplemented group

Parameter	Study Visits	Placebo (n = 17)	*Curcuma caesia* (Calebin A) (n = 18)	*p* Value
Body Weight (kg)	Screening	76.9 (11.08)	90.13 (14.75)	≤ 0.0001
	Day 90	79.11 (11.55)	81.94 (15.21)	
Body Mass Index (kg/m^2)	Screening	31.30 (3.31)	34.93 (4.53)	≤ 0.0001
	Day 90	32.37 (3.87)	31.82 (5.05)	
Waist Circumference (cms)	Screening	102.64 (10.62)	111.94 (11.12)	≤ 0.0232
	Day 90	102.58 (9.79)	107.20 (11.77)	

Values represent mean (standard deviation)

Table 4: Changes in serum fat metabolic markers from baseline to Day 90 in the Placebo and in *Curcuma Caesia* (Calebin A) supplemented group

Parameter	Study Visits	Placebo (n = 17)	*Curcuma caesia* (Calebin A) (n = 18)	*p* Value
HDL Cholesterol	Screening	36.45 (5.09)	38.65 (8.71)	≤ 0.0001
	Day 90	37.7 (4.81)	53.4 (4.91)	
LDL Cholesterol	Screening	136.4 (25.20)	130.71 (26.18)	≤0.0483
	Day 90	129.5 (26.56)	110.2 (27.00)	
Total Cholesterol	Screening	195.35 (29.89)	194.78 (34.43)	≤ 0.0470
	Day 90	190.1 (31.41)	178.0 (33.75)	
Triglycerides	Screening	130.46 (60.78)	143.44 (66.58)	≤ 0.0055
	Day 90	139.8 (70.60)	91.4 (49.35)	

Values represent mean (standard deviation)

FIGURES:

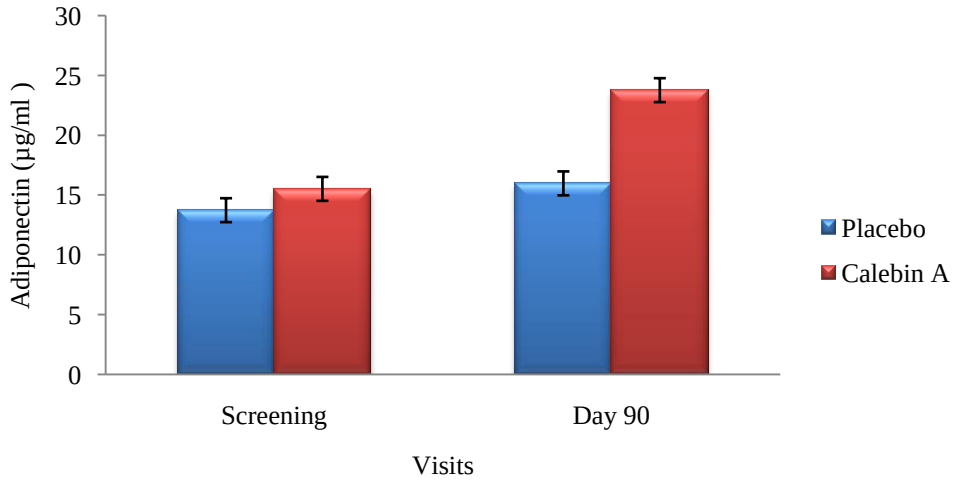

Figure 2: Serum adiponectin concentration (mean ± SD) of subjects supplemented with Calebin A and placebo were compared at screening and after 90 days. At the end of the study, Calebin A confers significant ($p \leq 0.01$) increase in adiponectin level in comparison with placebo.

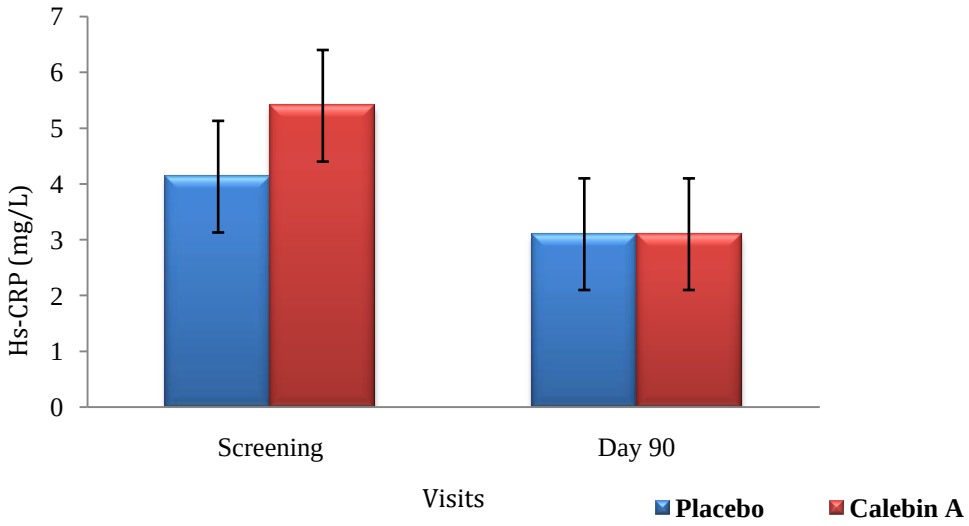

Figure 3: Hs-CRP concentration (mean ± SD) of subjects supplemented with Calebin A and placebo were compared at screening and after 90 days. At the end of the study, Calebin A confers significant ($p \leq 0.01$) decrease in Hs CRP level in comparison with placebo.

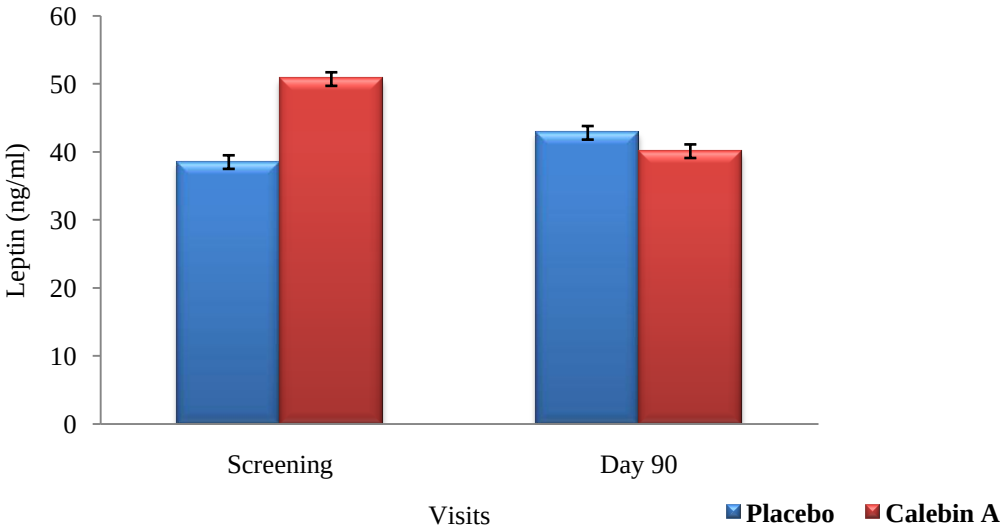

Figure 4: Serum leptin concentration (mean ± SD) of subjects supplemented with Calebin A and placebo at screening and after 90 days. At the end of the study, Calebin A confers significant ($p \leq 0.01$) decrease in leptin level in comparison with placebo.