

Effects of a preparation of *Phellodendron* and *Citrus* extracts on the joint and cardiovascular health of osteoarthritis patients: a pilot, double-blind, placebo-controlled study

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Abstract

Background

The objective of this clinical study was to study the safety and potential benefit of the dietary supplement NP 06-1 on joint health as well as cardiovascular protective properties in overweight and normal weight adults diagnosed with osteoarthritis of the knee.

Methods

The study was an 8-week, placebo-controlled, randomized, double-blind study with four groups, comparing the effects of NP 06-1 to placebo on overweight and normal weight subjects diagnosed with primary osteoarthritis of the knee. NP 06-1 (extracts of *Phellodendron amurense* bark and *Citrus sinensis* peel) or matching placebo was given in a dose of two capsules (370 mg each) twice daily. The outcome measures were the Lequesne Algofunctional Index (LAI) for joint function as well as biomarkers of inflammation and cardiovascular health. Analyses of variance were used to compare changes of physiological measures over the trial period.

Results

Eighty (80) subjects were enrolled and 45 subjects completed the study. The large number of dropouts was fairly evenly distributed among the groups, with the exception of the normal weight/placebo group which lost nearly twice as many participants as the other groups. No serious adverse events were reported. Treatment resulted in a statistical improvement in symptoms of physical pain and joint movement as measured by the LAI in both the overweight and normal weight groups compared to baseline and their respective placebo groups.

There was a reduction in CRP levels with treatment in the overweight participants compared to both the start of the study and to the perspective placebo

group. For the normal weight participants, there were significant reductions in CRP compared to baseline, but not to the perspective placebo group.

NP 06-1 generally improved lipid levels. Both the overweight and normal weight/treatment groups had significant reductions in triglycerides and LDL-cholesterol, as well as a significant increase in HDL-cholesterol compared to the perspective control groups.

Overall there were decreases in blood pressure in both overweight and normal weight treatment groups compared to perspective placebo groups. There was also a significant decrease in fasting glucose levels in the overweight/treatment group compared to the start of the study and to the overweight/placebo group. There was no change in fasting blood sugar for the normal weight groups.

Both overweight and normal weight treatment groups lost a significant amount of weight compared to their respective placebo groups. The overweight treatment group lost an average of 5% body weight after 8 weeks. There was no change in BMI in any group.

Conclusions

NP 06-1 appears to have beneficial effects on joint pain, movement and a marker for inflammation (CRP) compared to placebo for subjects with osteoarthritis of the knee. There were also significant improvements in cardiovascular risk factors; e.g. lipid levels, blood pressure and fasting glucose levels. NP 06-1 induced weight loss, which may have been a contributing factor to other improvements.

Background

Osteoarthritis, the most common form of arthritis, is characterized by degradation of articular cartilage, which manifests as joint pain and reduced mobility. The origin of the disease is unknown but obesity, joint injury, metabolic diseases,

bone and joint malfunctions, genetic factors and age have been implicated. Therapies for osteoarthritis include weight control, physiotherapy and pharmacological agents. Conventional drug treatments include analgesics, anti-inflammatory agents, disease modifying therapies, hyaluronic acid, intra-articular glucocorticoids and topical analgesic/anti-inflammatory agents.¹ More recently there has been a focus on nutritional support. Recent systematic reviews highlight the scientific evidence for potential nutritional and herbal preparations for those with osteoarthritis.^{2,3}

A systematic review of the literature covering obese subjects diagnosed with osteoarthritis of the knee concluded that osteoarthritis related disability could be significantly improved with a loss of over 5.1% body weight. A reduction in pain often also accompanied the weight loss, although this was not predictable.⁴

Obesity, by itself, represents a major, global health issue. Obesity has been defined using the Body Mass Index (BMI). The BMI is determined by dividing the body weight in kilograms by the height in meters squared. People with a BMI over 30 are categorized as obese. Those with a BMI over 25 but less than 30 are categorized as overweight. Increased body weight is associated with higher incidence of diabetes, hypertension and cardiovascular disease. This array of potential disease risks associated with excess weight has been coined as metabolic syndrome. Individuals with three or more of the components of central obesity (excess fat mainly in the abdominal area), hyperinsulinemia, dyslipidemia and hypertension are considered to have metabolic syndrome. Treatment involves lifestyle changes such as diet, exercise as well as pharmacological agents to address the various risk factors.⁵

The subject of this study, NP 06-1 (FlavoxineTM/CitrofenTM), Next Pharmaceuticals, Inc, Salinas, CA), is a proprietary dietary supplement formulation consisting of a blend of extracts of *Phellodendron amurense* tree bark and *Citrus*

sinensis (orange) peel standardized to berberine and polymethoxylated flavones, respectively.

Next Pharmaceuticals has previously conducted bioassay guided research on *Phellodendron amurense* tree bark resulting in a proprietary extract that has demonstrated analgesic and anti-inflammatory activity both *in vitro* and *in vivo*, in unpublished studies. Following this research, a product was developed (Nexrutine[®]) that has provided relief from pain and/or inflammation associated with over-exertion (i.e. sore muscles, sore joints, stiff joints) and osteoarthritis of the knee in several unpublished open-label clinical studies.

Citrus sinensis (orange) peel extracts contain bioflavonoids, including polymethoxylated flavones (PMFs). The latter compounds are known to be anti-inflammatory and to demonstrate benefits for the cardiovascular system (antioxidant, antithrombogenic, hypolipidemic effects). Kurowska and Manthey of the United States Department of Agriculture (USDA) reported that citrus PMFs caused significant reductions in total cholesterol ranging from 19 to 27%; and in very low density cholesterol (VLDL-C) and low density cholesterol (LDL-C), ranging from 32 to 40% in a hamster model.⁶ Research is ongoing on the potential antiatherogenic effects of citrus flavonoids.^{7,8} Next Pharmaceuticals has licensed US Patent Nos. 6,184,246 and 6,987,125 obtained by the USDA for actions described by PMFs.

NP 06-1 was formulated with the goal of combining the beneficial effects of both the phellodendron and orange peel extracts. The primary objective of this clinical study was to study the safety and efficacy of NP 06-1 compared to placebo in the management of joint pain and mobility caused by osteoarthritis of the knee. Secondary objectives were to study the effects on biomarkers related to inflammation and cardiovascular health. Both overweight and normal weight subjects were studied

to determine whether or not there might be a difference in benefits to these two groups.

Methods

Study Design

The study was a placebo-controlled, randomized, double-blind study with four groups. Forty overweight and forty normal weight subjects were enrolled into either treatment or placebo groups, with twenty subjects in each group as shown in Table 1. Subjects were recruited via advertisements at the University of Yaounde I Teaching Hospital, the Djongolo Baptist Hospital and through the public media. The IRB of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde in Cameroon approved the study and all subjects signed an informed consent. Dr. Julius Oben, Associate Professor of Nutritional Biochemistry at the University of Yaounde I, Cameroon was the principal investigator.

Inclusion Criteria

- Adult men and women, 25 to 60 years of age
- Diagnosed with primary osteoarthritis of the target knee using the American College of Rheumatology guidelines by the treating physician and confirmed by the clinical investigator.
- Body Mass Index between 25 kg/m² to 40 kg/m² (Groups 1 & 2 only - the Overweight Groups) OR Body Mass Index 18.9 kg/m² to 24.9 kg/m² (Groups 3 & 4 - the Normal Weight Groups)

Exclusion Criteria

- Morbid obesity BMI > 40 kg/m²
- Diagnosed with rheumatoid arthritis
- Joint replacements in any one of the knees
- Unable to walk without assistance
- Enrollment in another clinical study in the past 6 months
- Pregnancy, active infection, autoimmune disease, AIDS, HIV, or active hepatitis, active malignancy, diabetes requiring daily insulin management

Administration and Dosage

NP 06-1 is a proprietary product of Next Pharmaceuticals, Salinas, California. It is a blend of *Phellodendron amurense* (Rupr.) [Rutaceae] tree bark extract standardized to

a minimum of 50% berberine and *Citrus sinensis* (L.) Osbeck [Rutaceae] peel extract standardized to a minimum of 30% polymethoxylated flavones (PMF). It is sold under the trade names Flavoxine™ and Citrofen™.

Subjects were allocated into groups using a random number table and instructed to take two NP 06-1 capsules (370 mg formula per capsule) or matching placebo (identical red two-piece hard shell capsules) with food in the morning and at night (4 capsules per day) for a total of 8 weeks.

Subjects were instructed to avoid taking analgesics (a 5 day wash-out period prior to enrollment) or cholesterol lowering medications (a 30 day wash-out period prior to enrollment) during the study and to stay with their normal exercise and diet regimens.

Study Variables

1. Physical pain and joint movement as measured by the total score on the standardized Lequesne Algofunctional Index (LAI) questionnaire.⁹
2. Biomarkers for inflammation: C-Reactive Protein (CRP) and Red Blood Cell Sedimentation (RBC Sed).
3. Biomarkers of cardiovascular health: weight, BMI, triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, systolic/diastolic blood pressure and fasting glucose.

Data Collection

Pain, discomfort and flexibility of the knee were accessed at times 0, 4 and 8 weeks through the use of the LAI questionnaire completed by each subject at each study visit. Blood samples (8 ml) were collected by venous puncture at time 0, 4 and 8 weeks. Subjects were requested to come to the study center on the mornings of each site visit after a 12-hour fast. The concentrations of triglycerides, HDL-cholesterol, LDL-cholesterol and fasting glucose, were measured using commercial diagnostic kits (triglyceride Infinity, EZ HDL™ cholesterol, EZ LDL™ cholesterol,

Glucose Trinder) from SIGMA Diagnostics. CRP was measured using the Dade Turbitimer. RBC sedimentation was measured using the Westergren method.

Safety Assessment

Subjects were given three emergency telephone numbers to contact during the conduct of the study, if they had any adverse events or other concerns related to the study. Each subject was interviewed during site visits to solicit information on possible adverse effects they might have encountered. Participants were instructed to inform the investigator, if the reason for dropping out of the study was due to adverse effects.

Statistical Analysis

Analyses of variance, using repeated ANOVA, were used to compare changes of physiological measures over the trial period. The responses to the LAI questionnaire were analyzed using a one-way analysis of variance assuming continuous data and an ordinal logistic regression. All statistics were 2-tailed and significance was set at $p < 0.05$.

Results

Eighty (80) subjects were enrolled in the study and 45 subjects completed the study, as depicted in Table 1. The drop outs were high in number and their reasons are given in Table 2. The large number of dropouts was fairly evenly distributed among the groups, with the exception of Group 3 (normal weight/placebo group) which lost nearly twice as many participants as the other groups. No serious adverse events were reported.

LAI Scores

For Group 2 (overweight/treatment group), there were statistically significant decreases in LAI scores at 4 weeks (average of 29.9%) and 8 weeks (average of 46.1%) compared to baseline (both $p < 0.001$). In contrast there were no statistically significant changes from baseline for Group 1 (overweight/placebo group). Comparison of Groups 2 to 1 showed a significant difference between treatment and placebo at 4 ($p < 0.001$) and 8 weeks ($p < 0.01$).

For Group 4 (normal weight/treatment group) there were statistically significant decreases in LAI scores at 4 weeks (average of 32.6%) and 8 weeks (average of 31.7%) compared to baseline (both $p < 0.001$). There was no significant change from baseline for Group 3 (normal weight/placebo) after 4 weeks, but there was a significant change after 8 weeks ($p < 0.05$; average decrease of 19.6%). Comparison of Groups 4 to 3 showed a significant difference between treatment and placebo at both 4 and 8 weeks (both $p < 0.001$) (Tables 3 & 5).

Biomarkers of Inflammation

For Group 2 (overweight/treatment group), there were statistically significant decreases in CRP at 4 weeks (average of 28.4%) and 8 weeks (average of 48.8%) compared to baseline (both $p < 0.001$). There were smaller, but statistically significant, changes from baseline for Group 1 (overweight/placebo group). Comparison of Groups 2 to 1 showed a significant difference between treatment and placebo at 4 ($p < 0.05$) and 8 weeks ($p < 0.001$).

For Group 4 (normal weight/treatment group) there were statistically significant decreases in CRP at 4 weeks (average of 26.6%) and 8 weeks (average of 43.9%) compared to baseline (both $p < 0.001$). In contrast there were no statistically significant changes from baseline for Group 3 (normal weight/placebo group). There

were no significant differences between Groups 4 and 3 (normal weight/treatment and placebo) (Tables 3 & 5).

There were no significant changes in RBC sedimentation rate.

Cardiovascular Health

Weight / BMI

In Group 2 (overweight/treatment group), the subjects lost a significant amount of weight and their BMI was reduced compared to the start of the study ($p < 0.001$ at 4 and 8 weeks). They lost an average of 2.5 kg (5.5 pounds, 3.1% of body weight) after 4 weeks and an average of 4.2 kg (9.2 pounds, 5.1% of body weight) after 8 weeks. There were smaller, but statistically significant, changes in weight and BMI from baseline for Group 1 (overweight/placebo group). Comparisons of weight loss between Groups 2 to 1 revealed that the treatment group lost on average 3.7 times as much weight as the placebo group at 8 weeks (9.2 pounds versus 2.5 pounds) ($p < 0.001$). There was no significant difference in change in BMI between the treatment and placebo groups.

In Group 4 (normal weight/treatment group) there was a statistically significant loss of weight and BMI at 8 weeks ($p < 0.05$) compared to baseline. At 8 weeks, this group lost an average of 1.18 kg (2.6 pounds, 1.8% of body weight). Group 3 (normal weight/placebo group) also had a significant loss of weight and BMI after 8 weeks compared to the start of the study ($p < 0.01$). Comparisons of weight loss between Groups 4 and 3 revealed that the treatment group lost on average 1.5 times as much weight as the placebo group at 8 weeks (2.6 pounds versus 1.7 pounds) ($p < 0.01$). There was no significant difference in change in BMI between the treatment and placebo groups.

Total Cholesterol

For Group 2 (overweight/treatment group), there were statistically significant decreases in total serum cholesterol levels at 4 weeks (average of 15.6 %) and 8 weeks (average of 21.6%) compared to baseline (both $p < 0.001$). For Group 1 (overweight/placebo group), there were smaller, but statistically significant decreases in total serum cholesterol levels at 4 weeks (average of 7.2 %) and 8 weeks (average of 8.0%) compared to baseline ($p < 0.01$ and 0.05 , respectively). Subjects in the treatment group had a 2.7 times greater average decrease in total cholesterol in comparison to the placebo group. However the individual data was highly variable and the difference was not significant.

For Group 4 (normal weight/treatment group) there were statistically significant decreases in total serum cholesterol at 4 weeks (average of 7.3%) and 8 weeks (average of 9.7%) compared to baseline (both $p < 0.01$). For Group 3 (normal weight/placebo) there was a significant decrease at 8 weeks (decrease of 7.3%) but no significant change after 4 weeks. There were no significant differences between Groups 4 and 3 (treatment and placebo (Tables 4 & 5).

LDL-Cholesterol

For Group 2 (overweight/treatment group), there were statistically significant decreases in LDL-cholesterol levels at 4 weeks (average of 31.0 %) and 8 weeks (average of 44.6%) compared to baseline (both $p < 0.001$). For Group 1 (overweight/placebo group), there were smaller, but statistically significant decreases at 4 weeks (average of 13.8 %) and 8 weeks (average of 14.2 %) compared to baseline (both $p < 0.05$ and 0.05). Subjects in the treatment group had an average of 3.1 times greater decrease in LDL-cholesterol in comparison to the placebo group at 8 weeks. This difference was statistically significant ($p < 0.01$).

For Group 4 (normal weight/treatment group) there were statistically significant decreases in LDL-cholesterol at 4 weeks (average of 11.0%) and 8 weeks (average of 16.8 %) compared to baseline ($p < 0.05$ and 0.01 , respectively). For subjects in Group 3 (normal weight/placebo) there was a significant decrease in LDL-cholesterol at 8 weeks (decrease of 14.5%; $p < 0.05$); with no significant change after 4 weeks. Comparison of Groups 4 to 3 showed a significant difference between treatment and placebo at 8 weeks ($p < 0.01$) (Tables 4 & 5).

HDL-Cholesterol

For Group 2 (overweight/treatment group), there was a statistically significant increase in HDL-cholesterol levels at 8 weeks (average of 11.8 %) compared to baseline ($p < 0.05$). There was no significant change at 4 weeks. For Group 1 (overweight/placebo group), there were no statistically significant changes in HDL-cholesterol. Subjects in the treatment group had an average of 9 times greater increase in comparison to the placebo group at 8 weeks. This difference was statistically significant ($p < 0.001$).

For Group 4 (normal weight/treatment group) there was a statistically significant increase in HDL-cholesterol at 8 weeks (average of 3.9 %) compared to baseline ($p < 0.05$). There were no significant changes in HDL-cholesterol levels compared to the start of the study in Group 3 (normal weight/placebo). Comparison of Groups 4 to 3 showed a significant difference between treatment and placebo at 4 and 8 weeks (both $p < 0.05$) (Tables 4 & 5).

Triglycerides

For Group 2 (overweight/treatment group), there was a statistically significant decrease in plasma triglyceride levels at 4 weeks (average of 13.9%) and 8 weeks (average of 18.1 %) compared to baseline (both $p < 0.05$). Group 1 (overweight/placebo group) also had a statistically significant decrease in triglyceride

levels at 4 weeks and 8 weeks compared to baseline (both $p < 0.05$). However there was a significantly greater decrease in the treatment group in comparison to the placebo group at 8 weeks ($p < 0.001$).

For Group 4 (normal weight/treatment group), there was a statistically significant decrease in triglyceride levels at 4 weeks (average of 13.9%) and 8 weeks (average of 14.5 %) compared to baseline (both $p < 0.001$). For Group 3 (normal weight/placebo), there was a statistically significant decrease in triglycerides at 4 weeks but not at 8 weeks. Comparison of Groups 4 to 3 showed a significant difference between treatment and placebo at 4 and 8 weeks (both $p < 0.01$) (Tables 4 & 5).

Blood Pressure

For Group 2 (overweight/treatment group), there was a statistically significant decrease in systolic blood pressure at 4 weeks (average of 3.3%) and 8 weeks (average of 6.0 %) compared to baseline (both $p < 0.05$). There was also a statistically significant decrease in diastolic blood pressure at 4 weeks (average of 8.3%) and 8 weeks (average of 13.1 %) compared to baseline ($p < 0.01$ and 0.001 respectively). There were no statistically significant changes in either systolic or diastolic blood pressure in Group 1 (overweight/placebo). Comparison of Groups 2 to 1 showed a significant difference between treatment and placebo in diastolic blood pressure at both 4 and 8 weeks ($p < 0.05$ and 0.001 respectively) and in systolic blood pressure at 8 weeks ($p < 0.05$) (Table 4).

For Group 4 (normal weight/treatment group), there were no statistically significant changes in systolic blood pressure compared to the beginning of the study. However there were significant decreases in diastolic blood pressure at 4 weeks (average of 9.1% and 8 weeks (average of 11.6 %) compared to baseline ($p < 0.05$ and $p < 0.01$, respectively). For Group 3 (normal weight/placebo group), there was a

significant decrease in systolic blood pressure at 8 weeks ($p < 0.05$) but not at 4 weeks. This group had significant decreases in diastolic blood pressure at both 4 and 8 weeks ($p < 0.001$ and 0.01 , respectively). Comparison of Groups 4 to 3 showed a significant difference between treatment and placebo in diastolic blood pressure at both 4 and 8 weeks ($p < 0.05$ and 0.001 respectively). Comparison of Groups 4 to 3 also showed a significant difference in systolic blood pressure at 4 weeks ($p < 0.05$), but not at 8 weeks.

Fasting Glucose

In Group 2 (overweight/treatment group), fasting glucose levels decreased significantly at 4 weeks (average of 9.5%) and 8 weeks (average of 19.6 %) compared to baseline ($p < 0.05$ and 0.001 , respectively). There were no statistically significant changes in fasting glucose levels in Group 1 (overweight/placebo). Comparison of Groups 2 to 1 showed a significant difference between treatment and placebo at both 4 and 8 weeks (both $p < 0.001$).

In Groups 4 and 3 (normal weight/treatment and placebo groups), fasting glucose levels did not change statistically from the beginning of the study and there were no statistical differences between the two groups.

Discussion

NP 06-1 was safely administered to the trial participants in a dose of 4 capsules (1,480 mg) per day. The large number of dropouts, especially for Group 3 (normal weight/placebo group) is a weakness in the study. As a result, the comparisons between treatment and placebo for the normal weight participants are less reliable than those for the overweight groups.

The LAI scores indicated that NP 06-1 improved symptoms of physical pain and joint movement in both the overweight and normal weight groups compared to baseline and their respective placebo groups after 4 weeks of supplementation and to

an even greater degree after 8 weeks. The LAI index is derived from a standardized questionnaire that provides an indication of the severity of the disease by measuring pain/discomfort, maximum distance walked and activities of daily living.

The reduction in CRP with NP 06-1 for the overweight participants compared to both the start of the study and to the overweight placebo group indicates that it had an anti-inflammatory action. CRP levels have been linked to disease progression in patients with osteoarthritis and may reflect the degree of inflammation in the joint synovium. This inflammation may contribute to symptoms and to cartilage damage. CRP levels have been found to be elevated in obese and overweight patients, with a correlation between CRP levels and BMI being observed in those with osteoarthritis. This is consistent with our results. It is also consistent with the correlation between CRP levels and BMI observed in patients as risk for cardiovascular events (i.e. heart attack, stroke). However there are suggestions that the link between CRP levels and inflammation (synovitis) is not due to weight alone.¹⁰ The finding that NP 06-1 may decrease CRP levels, especially in overweight subjects, indicates that it may slow the progression of joint destruction as well as ameliorate symptoms.

NP 06-1 generally improved lipid levels compared to the start of the study and to the placebo groups. High triglycerides, total cholesterol and LDL-cholesterol levels, along with low HDL-cholesterol levels, have been established as indicators of risk for cardiovascular disease.¹¹ In this study, the overweight and normal weight/treatment groups had significant reductions in triglycerides and LDL-cholesterol compared to their perspective control groups. For HDL-cholesterol, there was a significant increase compared both to the start of the study and perspective placebo for both treatment groups. The greatest change in lipid levels was observed

for LDL-cholesterol in the overweight treatment group, which fell an impressive 44.6%.

Overall there were improvements (significant decreases) in blood pressure in both overweight and normal weight treatment groups compared to the start of the study and compared to perspective placebos. There was also a significant decrease in fasting glucose levels in the overweight/treatment group compared to the start of the study and to the overweight/placebo group. There was no change in fasting blood sugar for the normal weight groups.

Both overweight and normal weight treatment groups lost a significant amount of weight compared to the start of the study and to their respective placebo groups. The overweight treatment group lost an average of 5.1% body weight after 8 weeks. As previously mentioned, a systematic review of the literature covering obese subjects diagnosed with osteoarthritis of the knee concluded that osteoarthritis related disability could be significantly improved with a loss of over 5.1% body weight.⁴ The weight loss may also have provided an additive benefit with other test variables namely CRP and fasting blood sugar levels. A systematic review reported that found that for each 1 kg of weight loss, the mean change in CRP level was -0.13 mg/L (weighted Pearson correlation, $r = 0.85$).¹²

Conclusions

NP 06-1 has been shown in a placebo-controlled clinical study to offer several potential health benefits in normal and overweight subjects with osteoarthritis of the knee. These potential benefits include improvement of knee joint pain/flexibility scores as measured by the LAI score and a reduction in inflammation as measured using CRP levels. There were also significant improvements in cardiovascular risk factors; e.g. lipid levels, blood pressure and fasting glucose levels. Treatment-induced

weight loss may have been a contributing factor to these improvements. There appears to have been additional benefits to the overweight group compared to the normal weight group in decreases in CRP and fasting glucose. However the large number of dropouts in the normal weight placebo group made the comparisons for these groups less reliable.

Competing interests

This study was sponsored by Next Pharmaceuticals. Mr Garrison was Chairman of the Board and Miss Dolnick is employed by Next Pharmaceuticals. Dr. Chambliss and Mr. Kothari were compensated as consultants to Next Pharmaceuticals

Authors' contributions

All authors were involved in the design of the study, as well as analysis and interpretation of the data. The study was carried out by Dr. Oben, the Principal Investigator and Miss Enonchong, his assistant.

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Tables

Table 1 - Study Groups

Group #	BMI Category	Treatment	Enrollment (Completed)
Group 1	Overweight*	Placebo	20 (13)
Group 2	Overweight*	Active	20 (14)
Group 3	Normal weight†	Placebo	20 (7)
Group 4	Normal weight †	Active	20 (11)

*BMI 25 kg/m² – 40 kg/m²

†BMI 18.9 kg/m² – 24.9 kg/m²

Table 2 - Reasons given by Subjects for dropping out of the Study

Group #	Number of Subjects	Reason for drop out
Group 1	2	Reported no improvement in their condition
	1	Nausea and vomiting; Malaria attack
	1	Moved out of town
	3	No reason given
Group 2	1	Reported improvement as too slow
	1	Tested positive for hepatitis
	1	Moved out of town
	3	No reason given
Group 3	7	Reported no improvement in their condition
	1	Nausea
	1	Started weight management program
	1	Started fasting and stopped treatment
	3	No reason given
Group 4	1	Malaria attack
	1	Nausea
	1	Started fasting and stopped treatment
	6	No reason given

Table 3 - Body Weight, BMI, LAI scores, CRP levels & RBC sedimentation

Values at the start of the study (Time 0), after 4 weeks and after 8 weeks are means of data from individuals. % Δ values are percent mean change in value between time 0 and either 4 or 8 weeks. A negative value indicates a decrease and a positive number indicates an increase. P-value comparisons are between initial values at Time 0 and either 4 weeks or 8 weeks.

	Time 0	4 weeks	8 weeks	% Δ 0-4wks	% Δ 0-8wks	Δ 0-4wks	Δ 0-8wks
Group 1*							
Weight (kg)	85.0	83.8	83.8	-1.3	-1.4	p<0.001	p<0.01
BMI (kg/m ²)	31.1	30.7	30.7	-1.3	-1.4	p<0.001	p<0.01
LAI Score	1.24	1.17	1.19	-5.7	-4.0	NS	NS
CRP (mg/dl)	11.9	10.2	10.7	-14.8	-9.9	p<0.01	p<0.001
RBC Sed (mm/h)	13.6	13.5	13.6	-0.6	0.0	NS	NS
Group 2*							
Weight (kg)	81.7	79.2	77.5	-3.1	-5.1	p<0.001	p<0.001
BMI (kg/m ²)	31.7	30.7	30.1	-3.0	-5.1	p<0.001	p<0.001
LAI Score	1.17	0.82	0.63	-29.9	-46.1	p<0.001	p<0.001
CRP (mg/dl)	13.3	9.5	6.8	-28.4	-48.8	p<0.001	p<0.001
RBC Sed (mm/h)	12.6	13.0	12.9	10.3	9.1	NS	NS
Group 3*							
Weight (kg)	67.1	66.6	66.5	-0.4	-1.1	NS	p<0.01
BMI (kg/m ²)	24.0	23.8	23.8	-0.4	-1.2	NS	p<0.01
LAI Score	1.17	1.03	0.99	-12.0	-19.6	NS	p<0.05
CRP (mg/dl)	7.6	7.6	6.4	-0.8	-10.2	NS	NS
RBC Sed (mm/h)	12.4	12.7	12.7	3.1	3.1	NS	NS
Group 4*							
Weight (kg)	67.0	66.5	65.8	-0.8	-1.8	NS	p<0.05
BMI (kg/m ²)	24.8	24.7	24.4	-0.7	-1.7	NS	p<0.05
LAI Score	1.14	0.76	0.77	-32.6	-31.7	p<0.001	p<0.001
CRP (mg/dl)	11.5	8.4	6.4	-26.6	-43.9	p<0.001	p<0.001
RBC Sed (mm/h)	13.1	13.4	13.3	2.8	1.4	NS	NS

*Group 1 is the overweight/placebo group, Group 2 is the overweight/treatment group, Group 3 is the normal weight/placebo group, and Group 4 is the normal weight/treatment group.
NS= not significant

Table 4 - Lipid Levels, Blood Pressure, Fasting Glucose

Values at the start of the study (Time 0), after 4 weeks and after 8 weeks are means of data from individuals. % Δ values are percent mean change in value between time 0 and either 4 or 8 weeks. A negative value indicates a decrease and a positive number indicates an increase. P-value comparisons are between initial values at Time 0 and either 4 weeks or 8 weeks. The unit of measurement for lipids and glucose is mg/dl; for blood pressure is mmHg.

	Time 0	4 weeks	8 weeks	% Δ 0-4wks	% Δ 0-8wks	Δ 0-4wks	Δ 0-8wks
Group 1*							
Cholesterol	195.7	192.0	196.5	-7.2	-8.0	p<0.01	p<0.05
HDL	69.8	70.9	68.7	1.2	-1.3	NS	NS
LDL	89.3	75.4	77.0	-13.8	-14.2	p<0.05	p<0.05
Triglycerides	124.8	117.3	120.2	-6.3	-3.7	p<0.05	p<0.05
Systolic BP	130.8	132.1	132.9	1.0	1.6	NS	NS
Diastolic BP	81.8	78.3	79.5	-4.2	-2.8	NS	NS
Glucose	113.8	104.8	103.7	0.2	-10.6	NS	NS
Group 2*							
Cholesterol	194.5	202.3	197.9	-15.8	-21.7	p<0.001	p<0.001
HDL	69.7	74.0	83.4	4.8	11.8	NS	p<0.05
LDL	105.9	69.3	47.7	-31.0	-44.6	p<0.001	p<0.001
Triglycerides	118.4	97.5	91.9	-13.9	-18.1	p<0.05	p<0.05
Systolic BP	135.1	130.6	127.0	-3.3	-6.0	p<0.05	p<0.05
Diastolic BP	82.7	75.9	71.9	-8.3	-13.1	p<0.01	p<0.001
Glucose	73.4	68.9	71.6	-9.5	-19.6	p<0.05	p<0.001
Group 3*							
Cholesterol	197.3	197.0	197.3	-4.8	-7.3	NS	p<0.05
HDL	63.6	63.2	64.9	-0.6	6.8	NS	NS
LDL	123.6	115.9	105.2	-7.1	-14.5	NS	p<0.05
Triglycerides	86.0	82.7	82.7	-3.8	-6.8	p<0.05	NS
Systolic BP	127.0	122.1	125.3	-4.5	-5.3	NS	p<0.05
Diastolic BP	84.7	78.3	80.0	-3.8	-6.8	p<0.001	p<0.01
Glucose	57.6	56.7	57.6	-0.3	-0.0	NS	NS
Group 4*							
Cholesterol	197.0	197.2	197.0	-7.3	-9.7	p<0.01	p<0.01
HDL	67.3	67.9	70.0	0.74	3.9	NS	p<0.05
LDL	116.0	105.2	96.5	-11.0	-16.8	p<0.05	p<0.01
Triglycerides	88.7	76.4	75.9	-13.9	-14.5	p<0.001	p<0.001
Systolic BP	126.6	129.5	124.3	2.3	-1.8	NS	NS
Diastolic BP	81.2	73.8	71.7	-9.1	-11.6	p<0.05	p<0.05
Glucose	56.9	57.4	56.9	-0.9	-4.8	NS	NS

*Group 1 is the overweight/placebo group, Group 2 is the overweight/treatment group, Group 3 is the normal weight/placebo group, and Group 4 is the normal weight/treatment group.

NS=not significant. ¹mg/dl