# The French Maritime Pine Bark Extract Reduce Metabolic Syndrome Risk and Improve Body Composition in Obesity: A New Clinical Approach

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**Abstract**- Metabolic syndrome is a cluster of conditions which enhance the risk of metabolic and cardiovascular diseases such as diabetes mellitus, dyslipidemia, or hypertension. Obesity plays a pivotal role in the pathogenesis of metabolic syndrome. French maritime Pine bark extract (PBE) in addition to its antioxidant properties, has protective effects on metabolic syndrome component through several mechanisms. At present, there are few data on the net impact of PBE on metabolic syndrome factors in obesity. This trial report the results of 2-month period supplementation of 38 obese women received weight loss diet and PBE (150mg/day) or placebo. The metabolic syndrome parameters and body composition were assessed at the beginning and end of the study. The results showed PBE has significant protective effects on metabolic syndrome factors including central obesity, TG, HDL, BP and FBS ($P$<0.05), decrease metabolic syndrome risk in obesity and improve body composition. Thus, The PBE is considered as a new approach to obesity and metabolic syndrome prevention.



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**Keywords:** Pine bark extract; Weight loss; Obesity; Metabolic syndrome; Body composition

## Introduction

Metabolic syndrome refers to a clustering of condition related to the enhanced risk of cardiovascular diseases including central obesity, diabetes mellitus (or insulin resistance), dyslipidemia, together with hypertension (1).

According to the International Diabetes Federation (IDF) definition, a person when considered have the metabolic syndrome that has Central obesity (waist circumference ≥94 cm for males and ≥80 cm for females with ethnicity specific values) plus any two of the following four factors: 1) Raised triglycerides (≥150 mg/dL), 2) Reduced HDL cholesterol (<40 mg/dl in males and <50 mg/dl in females), 3) Raised blood pressure (systolic BP ≥130 or diastolic BP ≥85 mm Hg) and 4) Raised fasting plasma glucose (≥100 mg/dL), or previously diagnosed type 2 diabetes (2).

Metabolic syndrome basically is associated with central obesity. Central obesity increases visceral fat which is combined with a higher flux of free fatty acid derived adipose tissue into the liver via the splanchnic circulation. These result in very low-density lipoprotein (VLDL) synthesis, hypertriglyceridemia, more release of glucose from the liver, subsequently hyperinsulinemia and insulin resistance (3). Additionally, evidence demonstrated that visceral fat has higher capacity to secrete proinflammatory adipokines such as interleukin-6, tumor necrosis factor-α and C-reactive protein. These inflammatory cytokines have higher levels of metabolic syndrome patients (4). However, observations show that 5-10% weight loss through diet therapy and exercise (using anti-obesity drugs or not) can reduce all metabolic syndrome components as well as the risk of cardiovascular disease and diabetes (5,6).

Pine bark extract (PBE) with registered trade name

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Pycnogenol® is a specific blend of phenolic compounds, consisting of phenolic acids, catechin, taxifolin, and procyanidins extracted from the bark of the pine (Pinus pinaster) (7). The molecular mechanisms of action of PBE is not known well but seems that mainly be related to its antioxidant properties and PBE capacity in scavenging free radicals, reactive oxygen and reactive nitrogen species (8,9). Also, it has been demonstrated that PBE is able to influence the expression of target genes modified by cell redox status (9,10). Recently the effects of PBE have been investigated in various in vitro and in vivo as well as clinical studies (11,12). Additionally, the PBE has shown that has suppressive effects on NF-κB transcription factors, a key factor-mediated inflammatory process, and expression of genes involved in inflammation pathway (11). The anti-inflammatory and cardiovascular bioefficacy of maritime PBE is demonstrated in numerous inflammatory conditions (11,13-15). Also, recent studies have indicated the protective features of PBE on metabolic syndrome components such as fasting blood sugar (FBS), high-density lipoprotein (HDL) cholesterol, triglyceride (TG), and waist circumference (16). Human studies show that PBE is able to decrease hypertension and lower FBS and HbA1c significantly and improve cardiovascular and metabolic risk factors (17).

However, although the growing interest in PBE supplementation among recent studies, the only limited clinical trials data are available particular in obesity and preventive net effects of PBE on metabolic syndrome risk. In this context present study aimed to evaluate the synergistic and net effect of French maritime PBE supplementation along with a weight loss diet on metabolic syndrome risk factors and body composition in obese women.

## Materials and Methods

### Patients and supplementation

The present study was a Randomized Double-Blind Placebo-Control Clinical Trial (RCT). Fifty healthy obese women (BMI= 30-35 kg/m$^2$) aged 18-45 years old were enrolled in this study. Patients were informed about the aim of the study. At the start of study, a written informed consent of Tehran University Medical of Sciences (TUMS) was obtained from all subjects. Participants were divided into two randomly allocated groups (PBE or placebo). Subjects could withdraw from the survey for any reason at any time. Exclusion criteria included pregnancy, lactation or menopause, use of any medication or presence of any other clinical condition and failure to follow the regime. In the present study, 5 women in PBE group (1 for pregnancy, 1 for sensitivity and skin rash, 3 for unwillingness to cooperate) and 7 women in the placebo group (1 for surgery, 2 for migration, 4 for unwillingness to cooperate) excluded from the survey.

The PBE group received Tablets with 150 mg pine bark extract, manufactured by Source Naturals (California, USA) and the placebo group took one placebo tablets (contain starch powder) per day for 2 months with meal.

### Diet

All participants received diet consulting and educational program by a nutritionist. Everyone received a standard weight loss regime for two months (minus 500 calories) and advised not to change his or her physical activity during the intervening period. To calculate total energy expenditure (TEE)، Resting energy expenditure (REE) was measured by indirect calorimetry (MetaCheck, KORR Medical Technologies, Inc., Salt Lake City, UT) as usual protocol (18). The activity thermogenesis (AT) was assessed using the short-form version of the International Physical Activity Questionnaire (IPAQ) (19). Thermic Effect of Food (TEF) is calculated as no more than an additional 10% of the REE added to the sum of the REE and AT. For each participant TEE was calculated by the formula (TEE=REE+TEF+AT) (20). The energy of weight loss diet calculated by reducing 500 calories from TEE. Diet compositions are summarized in table 1.

**Table 1. Composition of diets**

| | |
|---|---|
| **Carbohydrate (% of energy)** | 57.3 |
| **Fat (% of energy)** | 16.9 |
| **Protein (% of energy)** | 29.2 |
| **SFA (% of energy)** | 7.2 |
| **MUFA (% of energy)** | 8.1 |
| **PUFA (% of energy)** | 9.1 |
| **Fiber (gr)** | 22 |

SFA, saturated fatty acids; MUFA, Monounsaturated fatty acids; PUFA, polyunsaturated fatty acids

**Measurements of anthropometric, laboratory, and body composition data**

Anthropometric parameters including weight, height, waist circumference, and hip circumference were measured according to standard protocol as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP). Body mass index (BMI) and waist to hip ratio (WHR) were calculated using weight (kg)/height (m2) and waist circumference (cm)/ hip circumference (cm) method respectively (21).

The weight was measured with minimal clothing and no shoes. The height was measured in standing position, without shoes, paired legs, and heels in tangent situation with the wall. Waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, by a stretch-resistant tape. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor (22,23). Ten ml blood samples were taken from subjects. Two ml of blood was poured into CBC tubes (containing EDTA). The rest of blood samples were used to evaluate FBS, TG, HDL, T3, T4, and TSH (22).

At the start and at the end of the study, body composition also was evaluated by Bioelectrical Impedance Analysis method (Tanita body composition analyzer, BC-418MA) included fat mass, fat-free mass, abdominal fat and total water of body. In addition, at the end of the study, adverse events were recorded.

**Statistical analysis**

For statistical analysis, SPSS 20.0 was used. Data are expressed as mean±SD. Kolmogorov-Smirnov distribution test was used for assessing normality. The paired *t*-test was used for comparisons within groups. For comparisons between groups ANCOVA test (analysis of covariance) was used. The test level for statistical significance of differences between both treatment arms was defined as $P \leq 0.05$ for all tests.

## Results

**General information**

Fifty volunteer participants based on inclusion criteria (female, BMI= 30-35 kg/m$^2$) were enrolled in this survey. Demographic and clinical properties of participants in the two groups are illustrated in table 2. There were no statistically significant differences in age, weight, height, or physical activity level among the PBE and placebo groups ($P>0.05$).

**Table 2. Demographic information**

| | Placebo (n=25) | Pine bark extract (n=25) | *P* |
|---|---|---|---|
| **Age (years)** | 37.3 (8.5) | 37.4 (8.8) | 0.97 |
| **Height (cm)** | 159.5 (4.7) | 159.8 (3.5) | 0.86 |
| **Weight (kg)** | 82.4 (6.3) | 83.3 (4.3) | 0.62 |
| **Physical activity level*** | 1.30 (0.08) | 1.31 (0.04) | 0.20 |

*Sedentary:1.3, low Active:1.5, Active: 1.8, Very Active: 2.0

**BMI and body weight**

A significant weight loss was observed in intervention, and placebo groups (4.58 and 3.72 kg respectively) and PBE group showed a more reduction compared to placebo group. In PBE group, BMI change was significant from 32.65 (1.7) kg/m2 to 30.87 (1.6) kg/m2 ($P=<0.001$) that was more than placebo group over 2 months follow-up. The changes in BMI and body weight were significant between groups at the end of study ($P<0.05$).

**Central obesity and fat distribution**

As shown, central obesity and fat distribution were assessed by the measure of waist circumference, hip circumstance, and WHR. In the present study, mean waist circumference was decreased significantly in both PBE and placebo groups after 2 months of supplementation (from 97.1 (9.4) cm to 89.8 (7.0) cm in PBE group and from 98.5 (8.2) cm to 92.2 (5.4) cm in the placebo group). Moreover, a reduction was found in hip circumstance in 2 groups with a decrease from 117.6 (4.6) cm to 111.5 (4.0) cm in the intervention group and 116.5 (5.4) cm to 109.3 (4.2) cm in control group. The decrease was statistically significant compared to baseline. WHR showed a negligible reduction in PBE group (from 0.827 (0.091) to 0.805 (0.059)) after 2-month PBE supplementation that was not significant statistically ($P=0.051$) (Table 3). WC showed greater reduction in PEB groups versus placebo-receiving group.

**Table 3. Weight, BMI, waist and circumstance, WHR, SBP, DBP, FBS, and TG**

| | | Pine bark extract (n=20) | Placebo group (n=25) | *P* [b] |
|---|---|---|---|---|
| **Weight (kg)** | **Before** | 83.3 (4.3) | 82.5 (6.5) | 0.65 |
| | **After** | 78.4 (4.00) | 78.8 (6.5) | 0.004 [c] |
| | **Differences** | -4.8 (1.34) | -3.7 (0.4) | 0.004 |
| | ***P*** [a] | <0.001 | <0.001 | |
| **BMI (kg/m2)** | **Before** | 32.6 (1.7) | 32.38 (1.9) | 0.67 |
| | **After** | 30.8 (1.6) | 30.92 (1.9) | 0.001 [c] |
| | **Differences** | -1.7 (0.2) | -1.46 (0.1) | 0.001 |
| | ***P*** [a] | <0.001 | <0.001 | |
| **Waist circumstance (cm)** | **Before** | 97.1 (9.4) | 98.5 (8.2) | 0.64 |
| | **After** | 89.8 (7.0) | 92.2 (5.4) | 0.23 [c] |
| | **Differences** | -7.2 (5.0) | -6.2 (5.9) | 0.58 |
| | ***P*** [a] | <0.001 | 0.001 | |
| **Hip circumstance (cm)** | **Before** | 117.6 (4.6) | 116.5 (5.4) | 0.49 |
| | **After** | 111.5 (4.0) | 109.3 (4.2) | 0.08 [c] |
| | **Differences** | -6.1 (1.6) | -7.1 (3.5) | 0.26 |
| | ***P*** [a] | <0.001 | <0.001 | |
| **WHR** | **Before** | 0.82 (0.091) | 0.84 (0.06) | 0.48 |
| | **After** | .80 (0.059) | 0.84 (0.05) | 0.007 [c] |
| | **Differences** | -0.21 (0.01) | 0.001 (0.007) | 0.14 |
| | ***P*** [a] | 0.05 | 0.84 | |
| **SBP (mm Hg)** | **Before** | 12.1 (1.2) | 11.5 (2.2) | 0.27 |
| | **After** | 10.0 (0.9) | 10.9 (1.5) | <0.001 [c] |
| | **Differences** | -2.1 (0.9) | -0.5 (1.5) | 0.001 |
| | ***P*** [a] | <0.001 | 0.18 | |
| **DBP (mm Hg)** | **Before** | 8.1 (1.1) | 8.0 (0.9) | 0.82 |
| | **After** | 7.3 (1.0) | 7.8 (0.9) | 0.06 [c] |
| | **Differences** | -0.8 (0.8) | -0.2 (0.9) | 0.084 |
| | ***P*** [a] | <0.001 | 0.2 | |
| **FBS ( mg/dl)** | **Before** | 89.3 (23.8) | 89.0 (14.3) | 0.96 |
| | **After** | 79 (10.9) | 86.6 (7.5) | 0.005 [c] |
| | **Differences** | -9.6 (15.2) | -2.3 (14.8) | 0.16 |
| | **P value** [a] | 0.01 | 0.5 | |
| **TG ( mg/dl)** | **Before** | 111.5 (41.8) | 118.6 (45.3) | 0.62 |
| | **After** | 110.5 (33.1) | 132.0 (42.8) | 0.03 [c] |
| | **Differences** | -1.0 (23.8) | 13.37 (28.28) | 0.10 |
| | ***P*** [a] | 0.85 | 0.07 | |
| **HDL ( mg/dl)** | **Before** | 41.9 (9.2) | 41.9 (7.0) | 0.98 |
| | **After** | 45.7 (8.5) | 40.0 (7.4) | 0.01 [c] |
| | **Differences** | 3.8 (8.0) | -1.9 (5.2) | 0.01 |
| | ***P*** [a] | 0.04 | 0.15 | |
| **Metabolic syndrome risk factors** | **Before** | 2.85(1.2) | 2.8 (1.3) | 0.95 |
| | **After** | 2.15(0.8) | 2.5 (1.1) | 0.14 [c] |
| | **Differences** | -0.7 (0.9) | -0.3 (1.0) | 0.25 |
| | ***P*** [a] | 0.005 | 0.2 | |

[a] paired samples *t*-test
[b] one way ANOVA
[c] ANCOVA test
BMI, Body Mass Index; WHR, Waist to Hip ratio; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FBS, Fasting Blood Sugar; TG, Triglyceride; HDL, High-Density Lipoprotein;

**Lipid profile (TG and HDL cholesterol)**

No significant differences were observed in the mean level of TG in PBE or control group when compared to baseline and after 2-month supplementation ($P>0.05$) but a very more reduction was seen in PBE group. However, TG changes between 2 groups were significant ($P<0.05$). HDL cholesterol levels were also significantly improved in the PBE group compared to baseline as increase from 41.9 (9.2) mg/dl at baseline to 45.7 (8.5) mg/dl at the end of study ($P<0.05$). In control group, the changes of HDL was not statistically significant ($P>0.05$).

**Blood pressure**

Systolic and diastolic blood pressures were monitored at the baseline and after 2 months of supplementation. The mean SBP decreased significantly ($P$<0.05) in the treatment group and placebo group. A similar significant reduction for DBP mean also was observed only in PBE group compared to baseline ($P$<0.05).

**Fasting blood sugar**

The FBS values improved significantly in the PBE group from 89.3 (23.8) mg/dl to 79 (10.9) after 2 months of receiving PBE ($P$<0.05). A slight decrease of FBS was found in the placebo group compared to baseline, but it was not statistically significant ($P$>0.05). Also, these changes were significant between groups.

**Body composition results**

As we can see in table 4, fat mass, free fat mass, abdominal fat and total body water show significant changes in treatment and placebo groups ($P$<0.05) with more improvement in PBE group.

**Table 4. Body composition**

| | | Pine bark extract (n=20) | Placebo group (n=25) | *P* [b] |
|---|---|---|---|---|
| **FM (kg)** | **Before** | 34.0 (2.6) | 32.9 (4.5) | 0.34 |
| | **After** | 31.0 (2.3) | 30.7 (4.7) | 0.03 [c] |
| | ***P*** [a] | <0.001 | <0.001 | |
| **FFM (kg)** | **Before** | 48.5 (3.2) | 48.9 (2.2) | 0.65 |
| | **After** | 47.7(3.1) | 47.7 (2.7) | 0.2 [c] |
| | ***P*** [a] | 0.009 | <0.001 | |
| **Abdominal Fat (kg)** | **Before** | 38.3 (3.7) | 36.2 (2.7) | 0.1 |
| | **After** | 36.3 (3.8) | 35.1 (3.0) | 0.4 [c] |
| | ***P*** [a] | <0.001 | 0.001 | |
| **Total water (% of body weight)** | **Before** | 43.0 (2.0) | 44.2 (2.2) | 0.1 |
| | **After** | 44.2 (2.4) | 44.9 (2.3) | 0.04 [c] |
| | ***P*** [a] | <0.001 | 0.001 | |

* paired samples *t*-test

** ANCOVA test

FFM: Free Fat Mass, FM: Fat Mass, REE: Resting Energy Expenditure

**Metabolic syndrome risk**

As data shown in table 3, the metabolic syndrome risk decreased only in supplementation group (from 2.85 (1.22) to 2.15(0.87)) which was statistically significant ($P$<0.05). Prevalence of the metabolic syndrome risk factors in the study subjects at inclusion 5/5 risk factors of the metabolic syndrome was present in all subjects as per inclusion criteria (Table 5).

**Table 5. Prevalence of the metabolic syndrome risk factors**

| | Risk factors present | Inclusion | Baseline | | At 2 months | |
|---|---|---|---|---|---|---|
| | | | Placebo | Pine bark extract | Placebo | pine bark extract |
| | | | Number (%) | Number (%) | Number (%) | Number (%) |
| **Metabolic Syndrome zone** | 5/5 | 100% | 3 (12) | 3 (12) | 1 (5.6) | 0 (0) |
| | 4/5 | 0 | 4 (16) | 6 (24) | 2 (11.1) | 2 (10) |
| | 3/5 | 0 | 6 (24) | 4 (16) | 5 (27.8) | 3 (15) |
| **Borderline Out of metabolic syndrome** | 2/5 | 0 | 9 (36) | 9 (36) | 9 (50) | 11 (55) |
| | 1/5 | 0 | 3 (12) | 3 (12) | 0 (0) | 4 (20) |
| | 0/5 | 0 | 0 (0) | 0 (0) | 1 (5.6) | 0 (0) |

**Safety**

During this study, all subjects except one did not disclose any side effects. One of the participants in the PBE group reported red skin rash while taking the PBE. No significant changes were observed in vital signs or blood parameters measured at baseline and after 2 months of treatment including CBC and Thyroid gland function ($P$>0.05) (Table 2).

## Discussion

Metabolic syndrome is a cluster of risk factors which increase the risk of cardiovascular diseases as well type 2 diabetes and stroke. Evidence well demonstrated that metabolic syndrome is associated with a proinflammatory condition (24). Obesity particularly central obesity is characterized by chronic low-grade inflammation and play a key role in the pathogenesis of metabolic syndrome (25). In addition, oxidative stress which is considered as a mechanism behind the risk of this syndrome, diabetes, and cardiovascular disease is associated with obesity (26).

The previous study demonstrated the beneficial effects of PBE in patients with metabolic syndrome or cardiovascular disease, but there is not a study regarding the combination of PBE with weight reduction in order to determine the net effects of PBE on metabolic risk factors and body composition in obese subjects. The current study is the first one that examines this effects (16,17).

In the present study, it was shown that 2 months of PBE administration in obese women who received weight loss regime significantly reduces weight, BMI, hip circumstance, WHR and exerts significant protective effects against metabolic syndrome factors including central obesity, TG, HDL, blood pressure, FBS, and significantly decreases metabolic syndrome risk in obese population. Moreover, it improves body composition.

The PBE a specific blend of procyanidins extracted from the bark of the pine has been demonstrated to contribute to antioxidant network and exerts radical-scavenging activity (9). In addition, Pycnogenol inhibits inflammatory response through suppressing of NF-κB-dependent gene expression (11). Also, Gallic Acid as an antioxidant component in PBE regulates body weight and glucose homeostasis without a change in food intake through activation of 5' AMP-activated protein kinase (AMPK) and proliferator-activated receptor-γ coactivator1α (PGC1α) in animal (27). Therefore, PBE can be beneficial in the context of glucose hemostasis and inflammation induced obesity, the conditions contributing to the pathogenesis of metabolic syndrome.

The results of present study show a greater reduction in BMI, weight, and WC in subjects who received PBE supplementation. Experimental evidence confirm these results and indicate that Pycnogenol enhances fat oxidation and lipolysis (28,29) and has preventive effects against metabolic syndrome (30). However, Belcaro *et al*., reported that administration of Pycnogenol for 6 months in patients with metabolic syndrome has limited effects on weight and BMI reduction (16). They also showed that Pycnogenol significantly reduces TG levels, blood pressure and increases HDL and significantly improves FBS which is parallel with our study. In another study, mean of HbA1c decreased by 0.8% in pycnogenol supplementation as well as fasting plasma glucose versus the control group (31). Moreover, experimental studies confirm these results and pine bark extract can significantly reduce levels of glycosylated hemoglobin and increase hepatic glycogen level (32). The known mechanisms of lowering FBS is that PBE inhibits α-glucosidase activity resulted in decrease of glucose absorption and postprandial hyperglycemia (27,33,34). Also, PBE significantly ameliorated oxidative stress such as thiobarbituric reactive substances, malonaldehyde, protein carbonyl, and glutathione and increase antioxidant enzymes including catalase, superoxide dismutase, glutathione S transferase, glutathione peroxidase, and glutathione reductase (32).

In the present study, 2 months of PBE supplementation showed a significant reduction in systolic and diastolic blood pressure but not in the placebo group. Based on previous observation, pine bark extract treatment showed 58.3% decrease in blood pressure of diabetic patients and 50% reduction in individual who take anti-blood pressure drugs. PBE is able to reduce endothelin-1 which contributes to endothelium contraction and hypertension (31). In this context, observation suggested that PBE acts as a vasodilator agent and can significantly improve endothelial function, venous tone, blood flow perfusion and decreases blood pressure and hypertension (35-38).

Additionally, in our study, PBE increased HDL significantly. There are evidence that PBE positively influences lipid profile in populations. Devaraj *et al*. observed a significantly improved blood lipid profile (decreased LDL) in young healthy subjects. Also, supplementation with PBE for 6 weeks significantly increased HDL which is similar to our results (39). Parallel with our results, Devaraj *et al*., showed that supplementation with a pine bark extract rich in polyphenols significantly reduces LDL-cholesterol and increases HDL-cholesterol levels in the blood as well as antioxidant activity (39). So, PBE exerts cardiovascular protective properties and can be considered as an effective compound in metabolic disorders.

Altogether, the results of this study suggested that PBE, an antioxidant and anti-inflammatory compound might play a role as adjuvant therapy and in combination with weight loss/ lifestyle modification can reduce the

risk of metabolic syndrome factors and improve body composition in order to fat mass reduction.

In conclusion, the current study suggests a role for PBE that along with weight loss can improve the cluster of features associated with metabolic syndrome (dyslipidemia, hyperglycemia, hypertension and elevated TG). The PBE acts through multiple mechanisms such as contributing to antioxidant network and suppression of inflammatory-mediated factors and gene expression levels. It seems that PBE as a natural and side effects free alternative compound can be noticed in high-risk subjects with changes in lifestyle. However, the clinical data for pharmaceutical usage are limited and clearly, for understanding of the molecular action of PBE further studies are needed.

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