Patented formulation for reducing liver and body fat
I. INTRODUCTION

This unique patent-protected, clinically studied natural formula helps people lose weight. It has the added benefit of reducing liver fat in women with fatty livers.

**TWO POWERFUL INGREDIENTS**

Xanthigen® is a breakthrough innovation that supports weight loss through the synergistic effect between brown seaweed and pomegranate seed oil based on a unique mechanism of action.

**IMPROVES LIVER FUNCTION**

Clinical evidence showed that Xanthigen® improves liver health and liver function, while its anti-inflammatory activity protects from pathologies related to overweight.

**DUAL EFFECT**

Xanthigen® supports weight loss, while at the same time protecting the liver and enhancing the overall health and wellbeing of overweight people.

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**What is Xanthigen®?**

Xanthigen® is Nektium’s patented, clinically studied proprietary formulation for weight management, consisting of pomegranate seed oil (*Punica granatum*) standardized to ≥ 35% punicic acid and brown seaweed extract (*Undaria pinnatifida*) standardized to ≥ 0.425% fucoxanthin.

**How does Xanthigen® work?**

Fucoxanthin stimulates lipolysis and inhibits lipogenesis\(^1\,^2\), while punicic acid helps reduce triglycerides and improves glucose tolerance and mitochondrial function in adipocytes\(^3\,^5\). The synergy between these two extracts promotes weight loss by increasing energy expenditure through browning of white adipose tissue by UCP-1 induction in mitochondria, suppressing adipocyte differentiation and lipid accumulation, reducing both, body and liver fat.

**Xanthigen® is protected**

Xanthigen® is protected by United States Patent 9,925,227: Compositions for treating obesity and method of using the same.
II. THE XANTHIGEN® INNOVATION

White adipose tissue (WAT) is the main storage of excess energy, primarily in the form of triglycerides, and an excessive increase in WAT leads to overweight and obesity. A functionally distinct adipocyte subset, called brown adipose tissue (BAT) liberates energy as heat (non-shivering thermogenesis), mediated primarily through Uncoupling Protein-1 (UCP-1 or thermogenin) in mitochondria.

Because of the high number of mitochondria and the presence of UCP-1, brown fat adipocytes liberate energy through heat production. Studies indicate that the activity of BAT is higher in lean people than in the overweight/obese population. Promoting BAT function by encouraging WAT to behave like BAT, has major potential to help combat obesity. Xanthigen® promotes BAT-like features in WAT, probably through the activation of UCP-1 in WAT mitochondria.

XANTHIGEN® MECHANISMS OF ACTION

Clinical evidence showed that Xanthigen® also improved the liver function in overweight, non-diabetic women over and above positive weight loss.

**MECHANISMS OF ACTION**

<table>
<thead>
<tr>
<th>BROWN ADIPOSE TISSUE</th>
<th>WHITE ADIPOSE TISSUE</th>
<th>LIVER</th>
<th>MUSCLE</th>
<th>METABOLISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT (energy expenditure)</td>
<td>WAT (fat storage)</td>
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<tr>
<td>Reduced waist circumference</td>
<td>Reduced visceral adipocytes</td>
<td>Reduced liver fat</td>
<td>Modified gene expression associated with insulin signaling, lipogenesis, cell proliferation, inflammation, adipogenesis, gluconeogenesis</td>
<td>Reduced basal systemic inflammation</td>
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<tr>
<td>Increased weight loss of 6-7%</td>
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<td>Reduced liver inflammation</td>
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<td>Increased stress resistance</td>
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<td></td>
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<td>Modulated insulin pathway genes</td>
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<tr>
<td>Effect</td>
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<tr>
<td>Fat burner</td>
<td>Weight loss</td>
<td>Liver protection</td>
<td>Anti-inflammatory</td>
<td>Antioxidant</td>
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</tbody>
</table>

Weight management
Xanthigen® has been studied for 16 weeks in 151 overweight adults and in several preclinical studies.

**XANTHIGEN® PROMOTES WEIGHT LOSS, BURNS EXTRA CALORIES AND REDUCES LIVER FAT**

The effect of Xanthigen® on body weight, body fat and burned calories (resting energy expenditure, REE), as well as on liver fat and liver function were investigated in 151 obese, non-diabetic women (113 with nonalcoholic fatty liver disease (NAFLD) and 38 with normal liver fat content (NFL))\(^{10}\).

In this double-blind, randomized, placebo-controlled 16-week study, a daily oral dose of 600mg Xanthigen® resulted in an average of 5-7kg weight loss, 4-5kg body fat loss, reduced liver fat and a significant increase in resting energy expenditure of 1612±3 317 kJ/24 h from 5.87±0.3 to 7.03±0.33kJ/min (p < 0.05) at 16 weeks\(^9\) through the induction of UCP-1\(^9\) in white adipose tissue. Furthermore, in the subset of women with NAFLD, Xanthigen® decreased blood pressure and improved liver function.
**Xanthigen® Suppresses Weight Gain, Fat Accumulation and Steatosis**

Xanthigen® was studied in mice on a high fat diet (HFD), supplemented with Xanthigen® (10g Xanthigen®/kg HFD). Body weight, hepatic lipid accumulation, obesity index and serum biochemical variables were analyzed and compared to control groups on a HFD and a normal diet (ND).

After 11 weeks, the HFD + Xanthigen®-treated animals gained significantly less weight and accumulated less adipose tissue than animals on the HFD without Xanthigen® supplementation. Furthermore, the HFD + Xanthigen® group showed a reduction in adiposity index, serum triglyceride (TG) levels and liver TG accumulation, with suppression of steatosis.

**PPARγ and AMPK** are proteins closely related to the metabolism of adipocytes. PPARγ is highly expressed in WAT, regulates fatty acid storage and glucose metabolism and is implicated in adipocyte differentiation, while AMPK plays an important role in adipose tissue function and stimulates ATP generating pathways. In order to better understand the anti-obesity effect of Xanthigen®, these two key proteins were studied in mice fed a HFD, supplemented with 2.5% Xanthigen. After 11 weeks of treatment, blood, adipose tissue, liver and kidney samples were collected and analyzed.

The results were compared to a control group fed with a HFD without Xanthigen® supplementation and another control group that was fed a normal diet (ND). Results show that Xanthigen® reduces serum and adipocyte leptin levels, inhibits PPARγ expression and stimulates the AMPK pathway, explaining the anti-obesity activity of Xanthigen®.

**The Anti-obesity Effect of Xanthigen®**

*Caenorhabditis elegans* (*C. elegans*) is a small nematode that conserves 65% of the genes associated with human disease, including genes responsible for key proteins involved in fat metabolism. Obesity in *C. elegans* is defined as deposition of fat (TG) stored as drops inside intestinal and skin cells. The anti-obesity-effect of Xanthigen® was studied in *C. elegans*, a useful model for the analysis of fat accumulation. The results demonstrated that Xanthigen® reduces fat deposits in wild-type worms about 13% (p<0.001). These *C. elegans* were fed fat oil that was dyed a red color to make it visible in their bodies. One group of them received Xanthigen® and the other not. The group that was fed Xanthigen® absorbed less dyed red oil, which means they ate less. Translated to humans, this indicates that taking Xanthigen® could lead to less fat accumulation.
IV. GENETIC STUDIES

The expression of 84 genes was studied in muscle cells C2C12. After Xanthigen® treatment, 3 genes were up-regulated and 6 down-regulated. The up-regulated genes are involved in lipogenesis, cell proliferation and inflammation while the down-regulated genes are related to inflammation, adipogenesis and gluconeogenesis. Thus, Xanthigen® may modulate gene expression associated with insulin signaling in muscle cells.

V. CONCLUSION

The Xanthigen® formulation, considered safe after a 90-day toxicological assay, may contribute to weight loss through activation of white adipose tissue to increase energy expenditure, leading to a significant reduction of body fat and body weight. Xanthigen® inhibits the differentiation of fat cells, reduces adipogenesis and gluconeogenesis, and may modulate genes related to insulin homeostasis in vitro and may suppress obesity in vivo.

VI. MANUFACTURING PROCESS

XANTHIGEN® RAW MATERIAL

Nektium’s Undaria pinnatifida blades are harvested by hand between May and July. The plants are cut from the main cultivation ropes and are transported to a processing facility on the same day, where the blades are bathed in hot water to remove small mollusks and epiphytic algae. This blanching causes the seaweed to turn from brown to green without losing nutritional properties or active compounds.

Nektium’s pomegranate seed oil is cold-pressed from pomegranate seeds.

DNA BARCODING: IDENTIFICATION OF SPECIES

Botanical raw material first undergoes macroscopic visual inspection to ensure it conforms with reference material. DNA barcoding, via the Royal Botanical Garden, Madrid, is used to positively confirm botanical identity. Additionally, UHPLC chromatographic profiles are used to confirm the presence of the characteristic marker compounds and to quantify the active compounds.

QUALITY ASSURANCE & CERTIFICATIONS

Xanthigen® is the result of high quality raw materials combined with meticulous manufacturing procedures. Nektium’s facilities and production processes strictly comply with cGMP (independently audited and certified annually) and rigorous quality control programs that ensure reliable and high quality production.

Nektium Pharma S.L. is authorized by the Spanish Health & Food Agency for the production of botanical and fruit extracts in conformance with RD 1712/1991 and Spanish Regulations.
VII. BIBLIOGRAPHY


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