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Beneficial Effects Of Palmitoleic Acid (Omega-7) on components of The Metabolic Syndrome, with particular emphasis on Improvements In Insulin Sensitivity

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BACKGROUND/INTRODUCTION

The purpose of this scientific summary is to highlight the broad and significant pharmacologic effects of Palmitoleic Acid (C16:1n7), or an Omega 7 fatty acid, which heretofore has been under-appreciated and minimally marketed on a global scale. As will be shown subsequently throughout this document, Omega 7 actually has broader and more potent positive effects than those seen with the Omega 3's, which have been highly studied for decades and are part of a large expanding market throughout the world. As such, Tersus Pharmaceuticals, the innovator of a new, highly purified form of Omega 7, believes that we are on the cusp of a "tipping point" of appreciation for the actions of this unique compound and is taking a lead role on a global scale to properly educate practitioners, patients, consumers, distributors and the overall market of natural products as to the significant role that this product can play in the improvement of healthcare for all of Society throughout the world.

The organization of this summary in all areas of highlighted pharmacologic actions follows the logical sequence of: a) cellular or in vitro data, followed by: b) animal model data and concluding with: c) effects in humans.

SCIENTIFIC EVIDENCE FOR THE BENEFICIAL EFFECTS OF OMEGA 7 IN THE METABOLIC SYNDROME – FOCUS ON INSULIN SENSITIVITY/RESISTANCE

There is currently a growing epidemic of the metabolic syndrome worldwide. The three main components which result in the manifestations of the metabolic syndrome include: 1) lipid derangements; 2) obesity; and 3) insulin resistance and/or Type 2 diabetes. It has been projected that there are 387 million people worldwide that either already have the diagnosis or who will soon develop the signs and symptoms of Type 2 diabetes.

This document will elucidate from multiple, respected international research groups, that Omega 7 has demonstrated positive activity and/or critically-beneficial mechanistic effects **on all three components of this syndrome**. Because the Ministry of Health in the UAE is largely focused on the actions against the insulin resistance component, this aspect will be addressed in detail first. The other two areas of discussion (lipid derangements and possible effects on obesity) will follow after this first section.

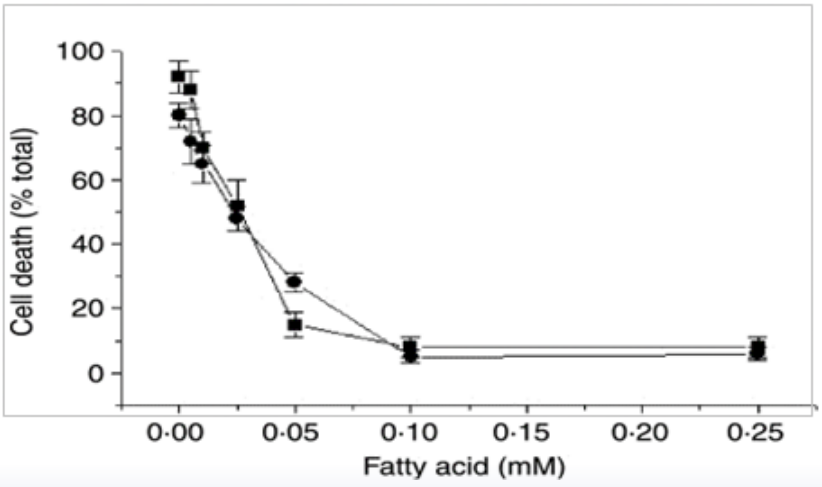
A. Laboratory Evidence for beneficial effects of Omega 7 in improving insulin sensitivity

It is well documented that Type 2 diabetes is the result of a loss of insulin sensitivity, or stated as the corollary, there is an increase in insulin resistance. This is often produced by beta cells of the pancreas that are less-than-normally responsive to circulating insulin levels, or loss of functioning beta cells, or a relative unavailability of beta cell receptors to the actions of insulin, often precipitated by the presence of increased amounts of abdominal fat deposits (i.e., obesity). All of these consequences work to form a vicious cycle that must be interrupted in order to work towards a reversal of these conditions. Failure to interrupt this cycle inexorably leads to proven elevations in morbidity and mortality from diabetes that eventually progresses to insulin-dependency (i.e., "burned out" Type 2 diabetics) and/or the development of cardiovascular disease manifestations.

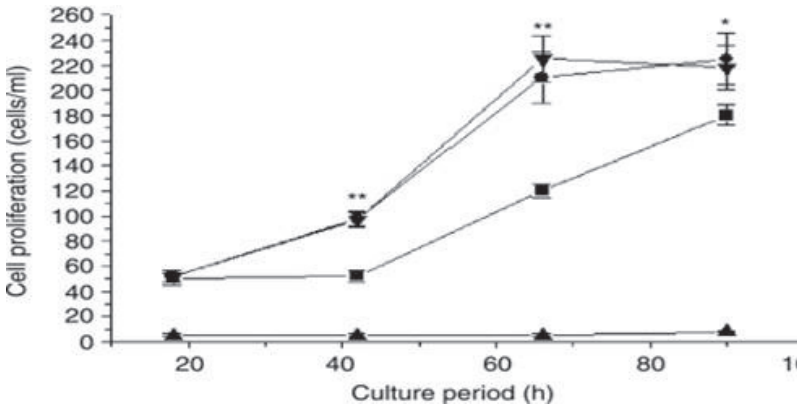
The actions of Omega 7 against insulin resistance are extremely interesting and myriad (multifactorial). The most direct, proven effects of Omega 7 against insulin resistance (or improving insulin sensitivity) relate to its direct effects of its ability to improve the survival of beta cells in the pancreas. The figure below shows the ability of Omega 7 to greatly improve beta cell death in a dose-dependent fashion and at extremely small concentrations after being exposed to the toxic effects of Palmitic Acid (C16:0). (More will be said about the universally negative effects of Palmitic Acid later on in this document.)

Prevention of Palmitate-Induced Pancreatic Beta Cell Death by Palmitoleic Acid and Its Ester (classic dose-dependent effects at low concentrations)

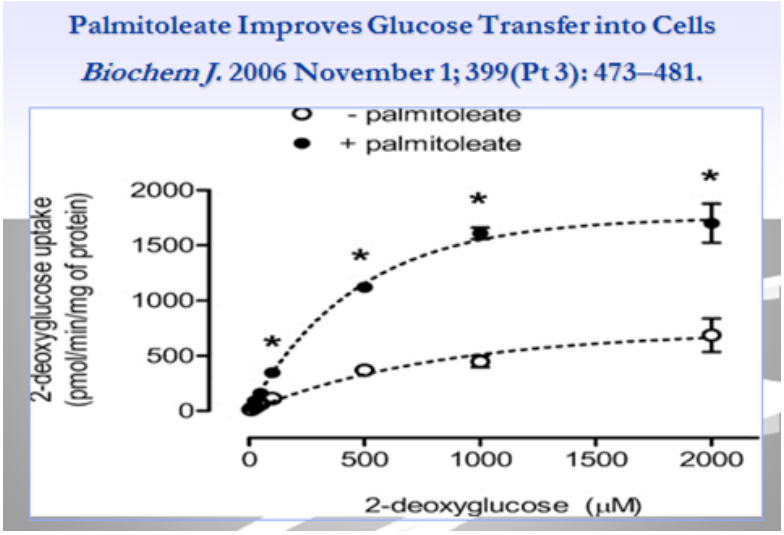
J Endocrinol. 2007 August;194(2):283-291



This negative effect of Palmitic Acid and the counteracting positive effects of Omega 7 are further highlighted in the next graph on the following page from the same reference. These results show several things. Firstly, Omega 7 free acid and ester (top two curves) alone stimulate beta cell proliferation. The control group is represented by the closed squares. Secondly, the potent negative effect of Palmitic Acid (closed triangles) virtually destroys upon immediate exposure the totality of beta cell growth. According to this data, such destruction occurs in less than a day.



Lastly, the figure below shows yet another possible beneficial mechanism from Omega 7 in the diabetic and insulin resistant state, in that Omega 7 (the ester form in this case) promotes glucose transport into cells. Obviously, these actions are akin to those of insulin, which helps drive glucose from the plasma intracellularly. In fact, researchers have documented that Omega 7 is equipotent with insulin and rosiglitazone pertaining to these actions.



B. So, is Omega 7 a hormone then?

The answer to this question is, "Yes". The outstanding work underpinning this concept came from Cao and his colleagues from Harvard University in 2008 (Cell. 2008; 134:933-44.) Out of 400 fatty acids screened, they determined that Omega 7 was a powerful lipid hormone (termed a "lipokine") that strongly stimulates muscle insulin action and inhibits hepatic steatosis (early indications as to possible anti-obesity actions). They also determined that Omega 7 (in the ester form) served as a communicator to distant organs and assisted in the regulation of metabolic homeostasis.

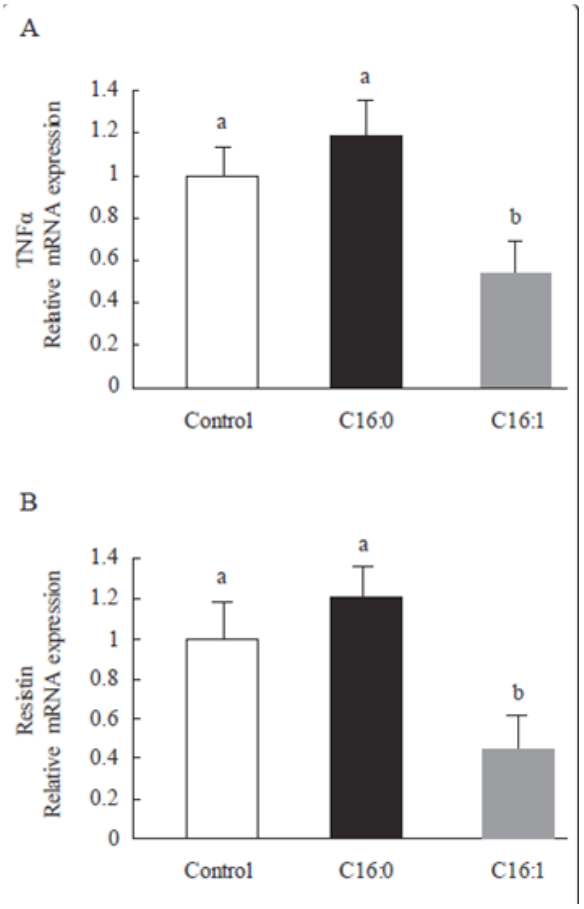
These facts have implications as to the potency and ultimate dose of Omega 7, in that extremely small doses and concentrations have been shown to result in magnified effects, which is one of the important definitions of a hormone's actions.

C. Confirmation of these results from other investigators – animal model investigations

In science, independent confirmation is the hallmark of identifying results that are real, significant and reproducible. The progression of examining the actions of Omega 7 were carried forth by a group of Japanese researchers as recently as last year (Lipids in Health and Disease. 2011; 10:120.). These researchers studied genetically-prone mice towards the development of insulin resistance the ultimate progression to diabetes and they took the step of administering Omega 7 exogenously and measuring the effects. The authors were searching for specific mechanisms of action to underpin the observations of Cao from Harvard. This was the first exogenous administration of Omega 7 in an intact animal in order to measure specific effects (as opposed to only correlating Omega 7 concentrations emanating from dietary sources).

Palmitoleic acid reduced body weight increase, ameliorated the development of hyperglycemia and hypertriglyceridemia, and improved insulin sensitivity. In addition, hepatic characteristics were significantly affected, as weight of the liver and hepatic triglyceride levels were lower in the palmitoleic acid group when compared to the control (vehicle and palmitic acid groups). Furthermore, palmitoleic acid down-regulated mRNA expressions of proinflammatory adipocytokine genes (TNF-alpha and resistin) in white adipose tissue and lipogenic genes (SREBP-1, FAS, and SCD-1) in liver.

The figure on the right shows the significant effects of Omega 7 in causing a reduction in TNF-alpha and resistin levels in these study animals. This particular animal model is bred to eventually develop diabetes and the actions of Omega 7 assisted in improving this progression. Also of note, which will be discussed in more detail in an upcoming Section, Omega 7 has direct counteracting effects to Palmitic Acid (C16:0). The effects of Palmitic Acid are universally negative, whereas the actions of Omega 7 are consistently positive when examined alone and are counteracting to the negative actions of its close structural cousin, C16:0.



Since inflammatory conditions have been associated with insulin resistance, the authors postulated that the translational endogenous reduction of TNF-alpha production was important to the anti-insulin resistance effects of Omega 7 administration. The actions of Omega 7 towards inhibiting SCD1 (stearoyl CoA desaturase), FAS (fatty acid synthase) and resistin will have further implications pertaining to possible effects on obesity parameters, such as the development of fatty liver and hepatic steatosis. These will be discussed in the Section dealing with possible weight loss indications.

D. Insulin sensitivity and anti-diabetic effects of Omega 7 in humans

Two different groups have carried the actions of Omega 7 to the next step and have correlated circulating Omega 7 ester levels with a clinical reduction in Type 2 diabetes development. Cao and his colleagues from Harvard set out to confirm their hypotheses regarding the positive "hormonal" effects of Omega 7 in a large population of >3,700 patients who were enrolled in the Cardiovascular Health Study from 1992-2006 (Annals of Internal Medicine. 2010; 153:790-9).

The investigators measured trans-palmitoleate (ester form) which comes exclusively from milk products and therefore was an indication of exogenous administration (as one would give a dietary supplement or a drug) and avoided the confounding facts related to endogenous generation of Omega 7 within the body (Omega 7 is produced within the body through conversion from C16:0 to C16:1).

Higher trans-palmitoleate levels were associated with slightly lower adiposity and, independently, with higher high-density lipoprotein cholesterol levels (1.9% across quintiles; P =0.040), lower triglyceride levels (-19.0%; P = 0.001), a lower total cholesterol–HDL cholesterol ratio (-4.7%; P = 0.001), lower C-reactive protein levels (-13.8%; P = 0.05), and lower insulin resistance (-16.7%, P = 0.001). Given that this "outcome" evaluation consisted of so many subjects and contained large statistical power, the collective effects of a reduction of inflammatory cytokines, such as CRP (C-reactive protein) as well as a lowered insulin resistance of between approximately 14-17% is extremely significant.

A group of German and Czech researchers in 2010 also correlated Omega 7 ester levels with insulin sensitivity in 100 humans who were at high risk for the development of diabetes (Diabetes Care. 2010; 33:405-7.). The researchers found that circulating Omega 7 ester levels independently correlated with the increase in insulin sensitivity in a concentration dependent manner.

E. Conclusions regarding Omega 7 and improvements in insulin sensitivity

We have seen from this brief review from multiple independent research groups that Omega 7 is positively associated with insulin sensitivity. These results have been corroborated amongst these publications and the results range from in vitro cellular data to standardized animal models to humans. Importantly, these effects go beyond the pharmacologic actions of the Omega 3's as in several of these analyses any independent contribution of other fatty acids to Omega 7's effects were ruled out.

It is unusual for a dietary supplement to have such a large volume of independent and respected research that universally supports and confirms its significant pharmacologic effects.

SCIENTIFIC EVIDENCE FOR THE BENEFICIAL EFFECTS OF OMEGA 7 IN THE METABOLIC SYNDROME – FOCUS ON LIPID DERANGEMENTS

In the Cao paper above, we have already seen that Omega 7 has a broad range of effects on serum lipids. It has been shown to increase HDL and to decrease LDL and triglycerides. These are obviously additional positive contributory factors to alleviating some of the manifestations of the metabolic syndrome, though the effects on insulin sensitivity appear on the surface to be much more significant (i.e., protective effects on beta cells, inhibition of inflammatory cytokines, correlations with human outcome data, etc.).

In nature, one of the richest sources of Omega 7 is contained in macadamia nuts (approximately 17-20%). Several studies have documented positive effects on lipid parameters from the controlled ingestion of macadamia nuts as part of the diet (Arch Intern Med. 2000; 160:1154-1158.).
In an informal evaluation of the actions of Omega 7 on serum lipids performed by Tersus also has corroborated these findings as shown in the Table below.

LIPID EFFECTS – CASE STUDIES

Subject	Age	Statin Use	Preventative Maintenance	HDL			LDL		
				Base	Tx	%	Base	Tx	%
Male	72	Yes	Yes	44	51	+16%	82	61	-23%
Male	67	No	No	36	44	+22%	119	110	-8%
Female	70	Yes	Yes	38	44	+16%	104	92	-12%
Male	70	Yes	Yes	33	38	+15%	NA	NA	NA
Male	54	No	No	43	48.5	+11.3%	224 (C)	192 (C)	-14%
Male				30	37	+23%	129	100	-22%

This informal set of case studies demonstrated an average increase in HDL of 17% following the administration of Omega 7 and also showed a decrease in cholesterol and/or LDL. These actions are consistent with what has been reported in more controlled environments from independent research.

A. Comparative potency of EPA versus Omega 7 on serum triglycerides

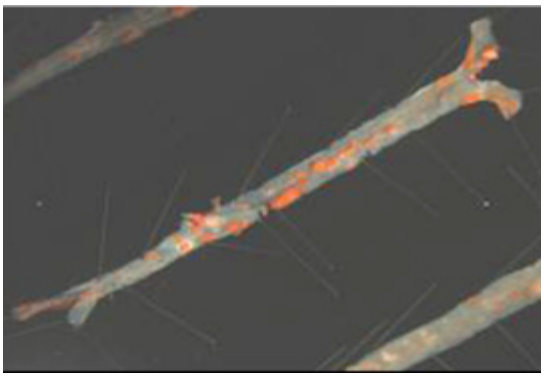
Two different research studies have evaluated the comparative actions of EPA (an Omega 3) and Omega 7 on serum triglycerides. EPA is widely known around the world as a compound that is active in this area of hypertriglyceridemia and concentrated forms are increasingly being developed by large multibillion dollar companies moving down the IND (FDA approved drug) route. These studies were performed by different groups, but they were done in the identical animal model of genetically-engineered mice that characteristically develop insulin resistance and diabetes. The references for these works are: (Metabolism Clinical and Experimental. 2006; 55:1590-8 and the previously cited work of (Lipids in Health and Disease. 2011; 10:120.).

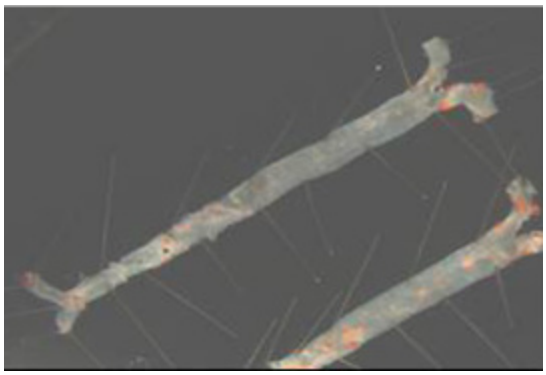
Interestingly, the comparative actions on serum triglycerides were equal, but the potency of Omega 7 in producing these equal results was 5-fold more on a mg/kg basis. The dose required to produce similar effects for EPA was 45 mg and for Omega 7 was 9 mg. Therefore, this indicates that Omega 7 has 5-fold the potency of EPA in the reduction of serum triglycerides as determined from these standardized animal models.

B. Omega 7 actions on arterial cholesterol deposition – possible prevention/regression of plaque formation

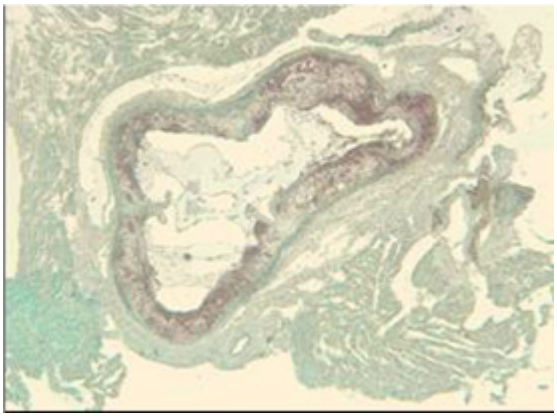
The formation, preservation and growth of atherosclerotic plaque in the arterial system are a significant contributor to human morbidity and mortality. This is a complex process, beginning in adolescence that involves oxidized LDL, foam cell deposition, smooth muscle involvement, calcium infiltration and influential inflammatory markers that exacerbate this pathophysiologic condition. Conceivably,

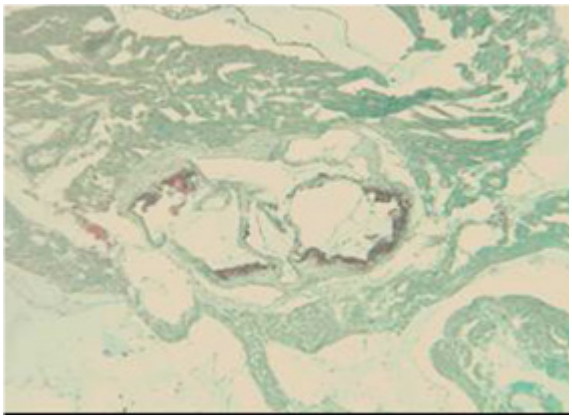
compounds, like Omega 7 that reduce LDL and increase the protective cholesterol of HDL could have an impact in this area. Antiatherogenic effects of the active ingredient in Provinal™ and Cardia7™ (an Omega 7) are pictured below from Apo-E mouse studies performed at the Cleveland Clinic in 2008.





Control (left) and treated animals (right) show dramatic reductions in aortic cholesterol deposition. Below are aortic root cross-sections in the same sequence, showing a virtual absence of atheroma formation after treatment with Omega 7. This study was repeated with identical results. Treatment caused 40-95% increases in HDL. Interestingly, and once again differentiating Omega 3's from Omega 7, they (Omega 3's) have shown no effect in this animal model (Atherosclerosis. 2008; 201:306-17.).





Perhaps more impressive are two other findings. Firstly, a consistent antiatherogenic effect was seen in all animals as measured by the aortic root lesion area (mm2). Secondly, in the Table below, Omega 7 showed superior effects in the identical animal model against rosuvastatin, which is the most potent statin on the market.

Additional animal and human research on Omega 7 has shown a lowering of LDL and triglycerides (as contrasted to Lovaza that increases LDL) and importantly, reductions in major inflammatory markers such as C-reactive protein and TNF-alpha, which assuredly play a role in cardiovascular disease etiology and could be a contributory mechanism in this antiatherogenic effect.

Table 1. Atheroma Area (mm^2) in the Aortic Root

	Control	Treatment
ProvinalTM Active Ingredient Omega 7	0.33 ± 0.09	0.18 ± 0.07**
Rosuvastatin (Crestor®)	0.36 ± 0.10	0.35 ± 0.10

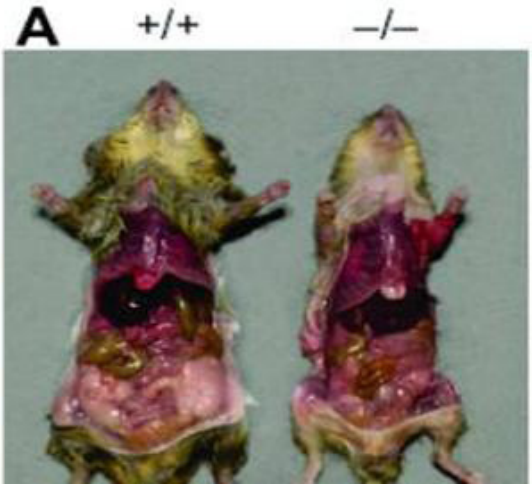
SCIENTIFIC EVIDENCE FOR THE BENEFICIAL EFFECTS OF OMEGA 7 IN THE METABOLIC SYNDROME – FOCUS ON ANTI-OBESITY & REDUCED STEATOSIS ACTIONS

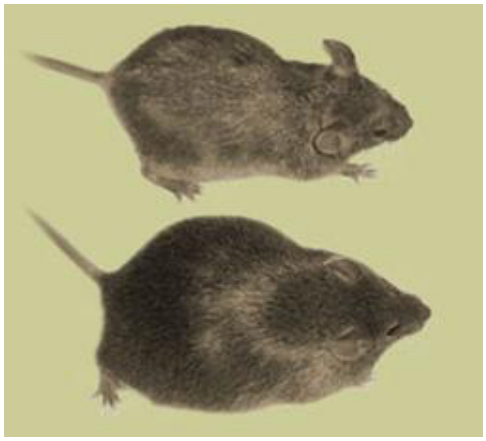
Previous studies already highlighted have shown an effect of Omega 7 on (inhibiting) FAS (fatty acid synthase), and (stimulating) adiponectin. FAS inhibition in the hypothalamus creates a satiety effect and diminishes one's desire to eat and is therefore an appetite suppressant. Interestingly, the impressive amount of data on nut administration and improvements in weight control as well as reductions in cardiovascular and Type 2 diabetes manifestations allows one to make the connection between these actions and the presence of Omega 7 in macadamia nuts as well as other fatty acids from these sources. As such, it would not be surprising that Omega 7 would have similar actions.

Adiponectin causes the efficient burning of fat in the liver and peripheral tissues.

Additionally, and consistent with the broad array of actions of Omega 7, it also inhibits SCD1 (stearoyl CoA desaturase). An inhibition of SCD1 is caused by Omega 7 in a dose-dependent fashion and is directly the opposite effect of Palmitic Acid (C16:0) that stimulates it. The two pairs of pictures below depict the impact of SCD1 inhibition. These pictures do not reflect administration of Omega 7, but demonstrate what happens when SCD1 is inhibited. Omega 7 is a strong inhibitor of SCD1.

The pictures below demonstrate the significant impact of blunting SCD1 effects by inhibiting fat deposition in the liver and stopping weight gain (below). The +/+ signs indicate the presence of activated SCD1 and the -/- signs indicate SCD1 is eliminated. The representative mouse that lost weight did so despite their continuing to overeat, implicating an increase in metabolism as the mechanism. Following an examination of the oxygen consumption in both groups, it was noted that metabolism was augmented both in waking hours and during sleep with the animals that had SCD1 inhibited. Interestingly, identical effects to the rats were seen from Omega 7 treatment in a study done at the Cleveland VA Hospital in 1998 that had a concentration of 40% Omega 7 as the treatment.





Critical Importance of the Compositional Makeup of Omega 7 Preparations

Tersus is not the first provider of Omega 7 on the market, but it is the first provider of a purified form of Omega 7 that intentionally has removed the accompanying concentration of the "bad fatty acid", Palmitic Acid (~1% or less). Currently, one can obtain Omega 7 from Sea Buckthorn sources, which is a plant source. Tersus obtains its purified Omega 7 from fish oil.

Sea Buckthorn sources contain approximately 26% of the "good fatty acid" of Omega 7 and have approximately 44% of the "bad fatty acid" of Palmitic. Thus, the compound that has exhibited negative actions is almost two-fold the concentration of the counteracting agent.

It is Tersus's belief that given the negative aspects of Palmitic Acid that have been summarized in this document (i.e., destruction of beta cells, stimulating SCD1, etc.) from multiple worldwide investigative groups that the a priori action should be to limit exposure to patients and consumers as much as possible from its detrimental effects. As an apropos caveat to this topic, the "Palm" in Napalm, the incendiary and inflammatory product used in wars, actually comes from Palmitic Acid as a major constituent. One can only speculate that if Palmitic Acid has this effect outside the body, what negative actions it is capable of producing when ingested inside the human system.

As such, the products from Tersus contain highly purified concentrations of Omega 7 while limiting the exposure to Palmitic Acid as much as possible.