Palmitoleic acid: An omega-7 fatty acid for inflammation & metabolic wellness

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Although the omega-3, -6, -7 and -9 category of fatty acids has grown consistently over the past few decades—and the worldwide market for fatty acids will grow from nearly $13.5 billion in 2018 to $17.5 billion by 2023[1]—the public and the dietary supplement industry know the least about the value of the omega-7 fatty acids. This article will explain the value of an *extremely well-researched* omega-7 fatty acid, *palmitoleic acid.*

Palmitoleic acid background

Palmitoleic acid naturally occurs as a common constituent of animal fats and plant seed oils, as well as a wide range of microorganisms, and is naturally produced in our bodies.[2] In fact, it is a common constituent of the glycerides of human adipose tissue and is released by adipocytes. It is present in all tissues but, in general, found in higher concentrations in the liver.

Research has shown that palmitoleic acid improves insulin resistance in skeletal muscle and liver and prevents hepatosteatosis (fatty liver disease). Palmitoleic acid treatment leads to improved glucose uptake, AKT phosphorylation and raises GLUT1 and GLUT4 protein levels in plasma membrane of skeletal muscle cells. Moreover, palmitoleic acid treatment also enhances AKT (i.e. a group of enzymes involved in several processes related to cell growth and survival), insulin receptor, insulin receptor substrate-1 and 2 protein phosphorylation in the liver and exerts cytoprotective effects in pancreatic β-cells.[3] All in all, palmitoleic acid plays an important role in human health and wellness.

Palmitic acid Background

Although palmitoleic acid is a valuable omega-7 fatty acid, another omega-7 known as palmitic acid is not. According to the World Health Organization (WHO), evidence is "convincing" that consumption of palmitic acid (a saturated fatty acid) increases the risk of developing cardiovascular disease.[4] The same year as WHO published its findings, Mensink et al.[5] published an important meta-analysis in *American Journal of Clinical Nutrition*, summarizing data from clinical trials on individual saturated fatty acids which clearly demonstrated that palmitic acid raised low-density lipoprotein (LDL) cholesterol—a strong indication of the mechanism by which palmitic acid increased cardiovascular disease risk. In any case, other published research[6] [7] has likewise indicated that palmitic acid has been identified as being adversely associated with most cardiovascular disease risk factors. In fact, palmitic acid has specifically been reported to be associated with risk of myocardial infarction.[8]

Consequently, it is important to make sure that the omega-7 fatty acid being used is primarily palmitoleic acid, not palmitic acid. One particularly good material I found is Provinal® (Tersus Life Sciences), a naturally sourced partially refined menhaden fish oil composed of not less than 50% palmitoleic acid and 1.5% oleic acid. The most important differentiating point of Provinal® is the *significantly lower content of palmitic acid* (less than 1%) as compared to 15% and 35% of other commercialized omega-7 products.

Palmitoleic acid research on metabolic syndrome parameters

According to the Mayo Clinic, metabolic syndrome (previously referred to as "insulin resistance syndrome," "cardiometabolic syndrome," or "syndrome X"[9]) is a cluster of conditions that occur together, increasing your risk of heart disease, stroke and type 2 diabetes. Central obesity and insulin resistance are thought to represent common underlying factors of the syndrome, which features a chronic low-grade inflammatory state. Metabolic syndrome is increasingly common, and up to one-third of U.S. adults have it. Therapeutic approaches that reduce the levels of proinflammatory biomarkers and address traditional risk factors are particularly important in preventing cardiovascular disease and, potentially, diabetes.[10] Palmitoleic acid can have value in addressing the aforementioned metabolic syndrome criteria.

Animal research on palmitoleic acid

A study[11] was conducted with sheep, examining the effects of palmitoleic acid (as Provinal®) compared to flaxseed oil and control on various parameters. Of particular interest, supplementation with palmitoleic acid also resulted in increasing bioavailability and significantly higher eicosapentanoic (EPA) and docosahexaenoic (DHA) acid accumulation in muscle and liver as compared to equal doses of flaxseed. *It should be noted that the increased bioavailability of EPA and DHA makes an excellent case for combining palmitoleic acid with these omega-3 fatty acids.*

In another study,[12] obese sheep were infused with palmitoleic acid (as Provinal®). The results were that palmitoleic acid reduced circulated insulin levels, improved insulin resistance, reduced intramuscular fat cell size, reduced total fat content within fat cells, and reduced weight gain by 77% (in a dose dependent manner as the blood concentration of palmitoleic acid increased).

In a third study,[13] palmitoleic acid was found to reduce body weight increase, ameliorate the development of hyperglycemia and hypertriglyceridemia, and improve insulin sensitivity, reduce hepatic lipid accumulation, and down-regulated mRNA expressions of proinflammatory adipocytokine genes in the liver of KK-Ay mice (a spontaneous model for studies of obese type 2 diabetes with low insulin sensitivity).

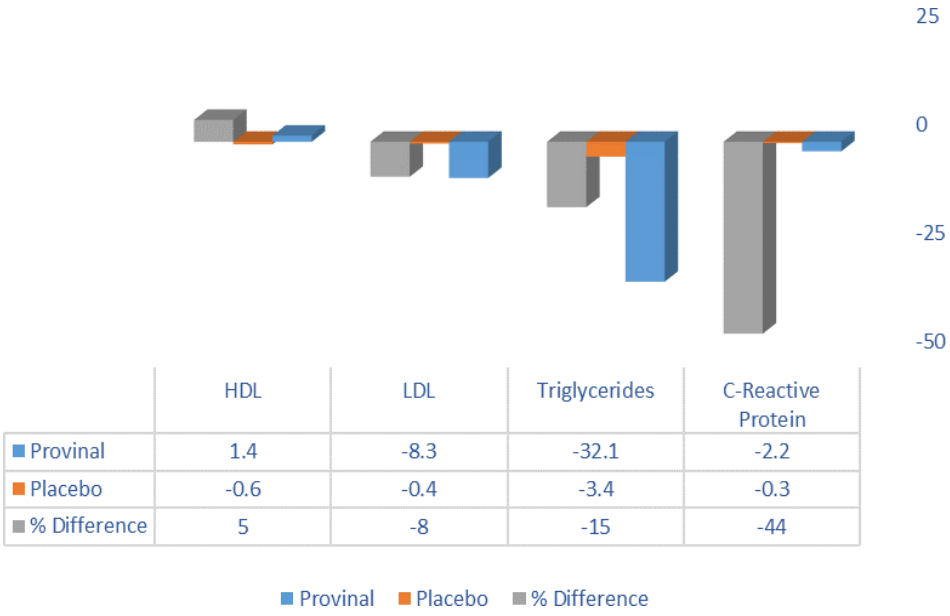
In a fourth study,[14] palmitoleic acid was found to decrease food intake (whereas olive oil did not), and elevate levels of the satiety hormone cholecystokinin (CCK) in male rats.

Human research on palmitoleic acid

A randomized, double-blind, placebo-controlled human trial[15] of purified palmitoleic acid supplementation (Provinal®) in adults with dyslipidemia and evidence of mild systemic inflammation (high-sensitivity C-reactive protein [CRP]). Subjects were randomly allocated to receive either 220.5 mg purified cis-palmitoleic acid as Provinal® (n = 30) or an identical capsule with placebo (1000 mg of medium chain triglycerides, n = 30) once per day for 30 days. Participants were asked to maintain their current diet. Serum lipids and CRP were drawn at baseline and study completion. Compared to control, the results at 30 days were significant changes in:

- CRP (-1.9 [-2.3 to -1.4] mg/L) 44% reduction,
- Triglyceride (-30.2 [-40.2 to -25.3] mg/dL) 15% reduction,
- Low-density lipoprotein (LDL) (-8.9 [-12.0 to -5.8] mg/dL) 8% reduction, and
- High-density lipoprotein (HDL) (2.4 [1.5, 3.3] mg/dL) 5% increase.

Researchers concluded that palmitoleic acid may be useful in the treatment of hypertriglyceridemia with the beneficial added effects of decreasing LDL and CRP and raising HDL.



A randomized controlled trial[16] of purified palmitoleic acid supplementation was conducted in adults with dyslipidemia and evidence of mild systemic inflammation (high-sensitivity C-reactive protein [hs-CRP] between 2 and 5 mg/L). Subjects were randomly allocated to receive either 220.5 mg of palmitoleic acid (n = 30) or an identical capsule with placebo (1000 mg of medium chain triglycerides, n = 30) once per day for 30 days. Participants were asked to maintain their current diet. Serum lipids and hs-CRP were drawn at baseline and study completion. Results were that at 30 days, there were significant mean reductions in CRP (-1.9 [-2.3 to -1.4] mg/L), triglyceride (-30.2 [-40.2 to -25.3] mg/dL), and low-density lipoprotein (LDL) (-8.9 [-12.0 to -5.8] mg/dL), and a significant increase in high-density lipoprotein (HDL) (2.4 [1.5, 3.3] mg/dL) in the intervention group compared with control. These changes equated to 44%, 15%, and 8% reductions in CRP, triglyceride, and LDL respectively, and a 5% increase in HDL compared with control. Researchers concluded that purified palmitoleic acid may be useful in the treatment of hypertriglyceridemia with the beneficial added effects of decreasing LDL and hs-CRP and raising HDL.

In a prospective cohort[17] of 3630 US men and women in the Cardiovascular Health Study, plasma phospholipid fatty acids, anthropometric variables, blood lipids, inflammatory markers, and glucose and insulin concentrations were measured between 1992 and 2006 by using standardized methods. In multivariable analyses, the results were that higher palmitoleic acid concentrations were independently associated with lower LDL cholesterol ($P < 0.001$), higher HDL cholesterol ($P < 0.001$), lower total:HDL-cholesterol ratio ($P = 0.04$), and lower fibrinogen ($P < 0.001$).

Researchers investigated[18] whether palmitoleic acid predicts insulin sensitivity in humans by examining the fasting fatty acid pattern in the plasma free fatty acid (FFA) fraction in 100 subjects at increased risk for type 2 diabetes. Insulin sensitivity was estimated during an oral glucose tolerance test (OGTT) at baseline and after 9 months of lifestyle intervention and measured during the euglycemic-hyperinsulinemic clamp (n = 79). Results were that circulating palmitoleic acid ($P = 0.007$) but not total FFAs ($P = 0.40$) correlated positively with insulin sensitivity, independently of age, sex, and adiposity. High baseline palmitoleic acid predicted a larger increase in insulin sensitivity. For 1-SD increase in palmitoleic acid, the odds ratio for being in the highest versus the lowest tertile of adjusted change in insulin sensitivity was 2.35 (95% CI 1.16–5.35). Researchers concluded that circulating palmitoleic acid

strongly and independently predicts insulin sensitivity, suggesting that it plays an important role in the pathophysiology of insulin resistance in humans.

A recent large meta-analysis[19] that pooled the findings from 16 multicentric prospective cohort studies from 12 countries (7 from the United States, 7 from Europe, 1 from Australia, 1 from Taiwan) performed new harmonized individual-level analysis for the prospective associations according to a standardized plan. In total, 63,682 participants with a broad range of baseline ages and BMIs and 15,180 incident cases of type 2 diabetes over the average of 9 years of follow-up were evaluated. After adjustment for potential confounders, including measures of adiposity (BMI, waist circumference) and lipogenesis (levels of palmitate, triglycerides), higher levels of palmitoleic acid were associated with lower incidence of type 2 diabetes.

In addition to metabolic syndrome parameters, research has also demonstrated that palmitoleic acid has efficacy in the treatment of dry eye syndrome. An open label proof-of-concept study[20] evaluated the effects palmitoleic acid (Provinal®) on dry eye syndrome (DES) on sixty patients. The primary objective was to evaluate the effects of palmitoleic acid administered daily over a 90- and 180-day period on the clinical management of dry eye syndrome caused by Meibomian Gland Dysfunction (MGD). Study results after three- and six-months treatment with 420 mg Provinal®, providing 210 mg palmitoleic acid, showed a significant improvement in Meibomian Gland function. Overall, there was a statistically significant reduction by 33% (p=0.0002) in the severity of symptoms as measured by the Standard Patient Evaluation of Eye Dryness (SPEED) score, partial blink was improved by 33% (p-value 0.0045) and 27% (p-value 0.0082) in the right and left eye respectively and tear break-up time (TBUT) was increased by 42% (p-value 0.0001) and 39% (p-value 0.0001) respectively for the right and left eye.

Dr. Brian J. Kane conducted an observational study[21] to assess the effect of palmitoleic acid (Provinal®) on 80 patients with evaporative dry eye disease (i.e. dry eye disease) over 11 months. The results were that, of the 80 patients, 74 experienced positive effects. Improved comfort was noted within 7-14 days, and improvements in osmolarity, symmetry binocularly and MGD (grade 2) was noted within 30 days. Within 60-90 days there were improvements in MGD (grade 3-4), with >50% improvement among all patients with MGD grade 4. Within 6 months there was positive Meibum production for all of the 74 patients.

Conclusion

The worldwide market for fatty acids is growing significantly. Animal and human research has demonstrated that palmitoleic acid (as Provinal®) has efficacy in reducing CRP, triglycerides and LDL, while increasing HDL. Likewise, palmitoleic acid has been shown to improve insulin sensitivity and help reduce total fat content within fat cells and reduce weight gain. In addition, palmitoleic acid has shown benefit in the treatment of dry eye syndrome.

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