Hydroxypropylmethylcellulose, Cetylated Fatty Acids and Weight Loss

Hydroxypropylmethylcellulose and Modified Cellulose-Based Polysaccharides of Plant Origin

Hydroxypropylmethylcellulose (HPMC; CAS No. 9004-65-3) is a term that identifies a class of odorless and tasteless synthetic modifications of naturally occurring plant-derived polysaccharides that are water soluble at typical ambient temperatures,[1,2] highly viscous at higher temperatures,[1,2] very poorly digestible *in vivo*,[3,4] nonfermentable *in vivo* and *in vitro*[3] and highly hydroscopic *in vivo*.[3] Adding powdered HPMC to human foods in the presence of water at body temperature produces a highly viscous substance.[5]

Hydroxypropylmethylcellulose polymers consist of repeating units of $C_6H_7O_2$ that carry varying numbers of methyl (CH_3) and propylmethyl ($CH_2CHOHCH_3$) side groups.[1,2] Depending on the number of specific side groups present, these various compounds differ in gelation temperature, viscosity, flexibility and degree of hydration.[1,2,6,7] The variety of variants has resulted in a number of synonyms being associated with these compounds: carbohydrate gum; cellulose hydroxypropyl methyl ether; hydroxypropyl methylcellulose (HPMC); hydroxypropylmethylcellulosum; hypromellose; isopto alkaline; isopto frin; isopto plain; isopto tears; propylene glycol ether of methylcellulose; methyl hydroxypropyl cellulose; methylhydroxycellulosum).[1] The US Food and Drug Administration (USFDA) allows the inclusion of plant-derived HPMC in foods and dietary supplements intended for human consumption when added as an emulsifier, film former, protective colloid, stabilizer, suspending agent, thickener, adhesive or coating.[8-11]

In men and women with moderate hypercholesterolemia, supplementing the diet with HPMC (2500 mg, dissolved in water, twice daily) for 2 to 4 weeks has reproducibly produced significant 5% to 10% additional reductions in serum total cholesterol and low-density lipoprotein-associated cholesterol concentrations, even in individuals on long-term stable HMG-reductase inhibitor therapies and regardless of whether the HPMC was consumed with meals or between meals.[12,13] These investigators concluded that because HPMC is resistant to fermentation in the human gut, the hypocholesterolemic effect resulted from binding of cholesterol (of both exogenous and endogenous origins) to the highly viscous HPMC substance within the gut and its transportation into the stool.

In a series of double-blind, randomized, placebo-controlled experiments that studied the effects of dietary HPMC in men and women with fasting hyperglycemia ("prediabetes"), the addition of either 4 or 8 g of HPMC to an oral bolus of 75 g of carbohydrates produced significant 10% to 30% decreases in the absorption of the glucose in the carbohydrate bolus during the first 2 hours post-ingestion.[14-16] These decreases were accompanied by significant reductions in postprandial insulin secretion.[14] In contrast, adding 1 g or 2 g of HPMC had no effect on the absorption of the glucose in the carbohydrate bolus during the first 2 hours post-ingestion.[15,16] In addition to supporting

healthy glucoregulation, HPMC supplementation could contribute to intentional weight loss: an adult male weighing 100 kg and 180 cm tall, restricting the daily diet to 2600 kcal (half as carbohydrate) in order to achieve a weight loss of 2 kg per month,[17] could experience an additional daily caloric deficit of between 130 and 390 kcal that could produce an additional loss of 1 kg in 10 to 30 days; an adult female weighing 80 kg and 165 cm tall, restricting the daily diet to 1750 kcal (half as carbohydrate) in order to achieve a weight loss of 2 kg per month, could experience an additional daily caloric deficit of between 90 and 270 kcal that could produce an additional loss of 1 kg in 14 to 40 days.

The results of a double-blind, randomized, placebo-controlled trial of the effects of a proprietary blend of plant-based polysaccharides, esterified fatty acids, pomegranate extract, mixed polyphenols, ellagic acid, β-carotene, and *Aphanizomenon flosaquae* extract on obese adult men and women are consistent with these calculations.[18] In the absence of dietary restrictions or prescribed increase in physical activity, the addition of the supplemental blend (270 mg or 540 mg twice daily) to meals for 8 weeks produced statistically significant averages of 5.25 kg and 6.5 kg more weight loss, respectively, than was produced by dietary supplementation with placebo. These greater amounts of weight loss were accompanied by significantly greater reductions in total body fat, waist circumference and hip circumference. No clinically significant adverse reactions were reported to have occurred during this study.

Because it has found the inclusion of plant-derived HPMC in foods and dietary supplements intended for human consumption to be safe, the US Food and Drug Administration (USFDA) allows the inclusion of plant-derived HPMC in foods and dietary supplements intended for human consumption when added as an emulsifier, film former, protective colloid, stabilizer, suspending agent, thickener, adhesive or coating.[8-11] The JECFA has determined that there is no evidence that modified celluloses, including HPMC variants, possess mutagenic, carcinogenic, teratogenic or developmentally harmful activities and that their inclusion in human foods is safe.[7]

After 3 months of oral supplementation with 20 mg of HPMC per kg body weight, mice, rats, beagle dogs and cynomolgus monkeys (*Macaca fascicularis*) exhibited no signs of toxicity.[19] No animals endured soft or loose stools, icterus, abnormal urine color or turbidity, altered food intake, abnormal weight gain or loss, hemolysis, or changes in red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin content, mean corpuscular hemoglobin concentration, hematocrit, reticulocyte count, total leukocyte count, differential leukocyte count, platelet count, mean platelet volume, blood smear morphology, serum concentrations of hemoglobin, glucose, total protein, cholesterol, triglycerides, urea nitrogen, albumin, globulin, creatinine, total bilirubin, potassium, phosphorus, chloride, sodium, or calcium, serum activities of aspartate aminotransferase, alkaline phosphatase, or alanine aminotransferase, or urinary excretion of protein, bilirubin, glucose, blood, acid, ketones, urobilinogen, phosphorus, calcium, sodium, creatinine, chloride, or potassium. Gross and histologic examination revealed no abnormalities in the adrenal glands, bone marrow, esophagus, Harderian glands, cecum, colon, lungs, ovaries, sciatic nerve, salivary gland, skin, spleen, thymus, trachea, vagina,

thoracic aorta, brain, eyes, heart, larynx, pharynx, lymph nodes, pancreas, pituitary gland, seminal vesicles, duodenum, jejunum, ileum, stomach, thyroid gland, urinary bladder, bone, epididymides, gall bladder, kidneys, liver, mammary gland, parathyroid gland, prostate gland, skeletal muscle, spinal cord, testes, tongue, uterus, or cervix, and organ weights were unaffected. The same amount of HPMC also has been reported to exert no reproductive, developmental or teratogenic effects in rats or rabbits.[20]

A dose-ranging 90-day study in rats demonstrated complete lack of detrimental effects of the oral consumption of up to 1020 mg per kg of body weight, although 2100 mg per kg of body weight produced mild growth retardation.[21] Variables that were unaffected by HPMC consumption included stool consistency, urine color and turbidity, food intake, growth rate, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin content, mean corpuscular hemoglobin concentration, hematocrit, reticulocyte count, total leukocyte count, differential leukocyte count, platelet count, mean platelet volume, blood smear morphology, serum concentrations of hemoglobin, glucose, total protein, cholesterol, triglycerides, phospholipids, urea nitrogen, albumin, globulin, creatinine, total bilirubin, potassium, phosphorus, chloride, sodium, or calcium, serum activities of lactate dehydrogenase, creatine phosphokinase, aspartate aminotransferase, alkaline phosphatase, or alanine aminotransferase, urinary excretion of protein, bilirubin, glucose, blood, acid, ketones, urobilinogen, phosphorus, calcium, sodium, creatinine, chloride, or potassium, gross and histologic appearance of the adrenal glands, bone marrow, esophagus, Harderian glands, cecum, colon, lungs, ovaries, sciatic nerve, salivary gland, skin, spleen, thymus, trachea, vagina, thoracic aorta, brain, eyes, heart, larynx, pharynx, lymph nodes, pancreas, pituitary gland, seminal vesicles, duodenum, jejunum, ileum, stomach, thyroid gland, urinary bladder, bone, epididymides, gall bladder, kidneys, liver, mammary gland, parathyroid gland, prostate gland, skeletal muscle, spinal cord, testes, tongue, uterus, or cervix, and organ weights.

Conclusions

- Dietary supplementation with high-viscosity plant-based polysaccharides (HPMC) reduces the efficiency of the absorption of lipids and glucose from the human gastrointestinal tract.[12-16]
- Dietary supplementation with a proprietary blend of a mixture of modified cellulose-based polysaccharides of plant origin, esterified fatty acids, pomegranate extract, mixed polyphenols, ellagic acid, β-carotene, and *Aphanizomenon flosaquae* extract induces fat loss in humans.[18]
- Daily dietary supplementation with 1080 mg of a proprietary blend of a mixture of modified cellulose-based polysaccharides of plant origin, esterified fatty acids, pomegranate extract, mixed polyphenols, ellagic acid, β-carotene, and *Aphanizomenon flosaquae* extract induces fat loss in humans.[18]
- Dietary supplementation with a proprietary blend of a mixture of modified cellulose-based polysaccharides of plant origin, esterified fatty acids,

pomegranate extract, mixed polyphenols, ellagic acid, β-carotene, and *Aphanizomenon flosaquae* extract induces weight loss in humans.[18]

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- Dietary supplementation with a proprietary blend of a mixture of modified cellulose-based polysaccharides of plant origin, esterified fatty acids, pomegranate extract, mixed polyphenols, ellagic acid, β-carotene, and *Aphanizomenon flosaquae* extract supports healthy body composition in humans.[18]
- Daily dietary supplementation with 1080 mg of a proprietary blend of a mixture of modified cellulose-based polysaccharides of plant origin, esterified fatty acids, pomegranate extract, mixed polyphenols, ellagic acid, β-carotene, and *Aphanizomenon flosaquae* extract supports healthy body composition in humans.[18]
- Daily dietary supplementation with 1080 mg of a proprietary blend of a mixture of modified cellulose-based polysaccharides of plant origin, esterified fatty acids, pomegranate extract, mixed polyphenols, ellagic acid, β-carotene, and *Aphanizomenon flosaquae* extract is safe.[8-21]

Cetylated Fatty Acids

In a model system intended to mimic typical stomach and intestinal environments, negligible amounts of cetylated fatty acids were hydrolyzed, suggesting that a large proportion of ingested cetylated fatty acids are available for absorption intact.[22] The bioavailability of cetylated fatty acids was examined in rats given oral boluses of cetylated fatty acids (similar in composition to those contained in the Celadrin™ product). Following the ingestion of the cetylated fatty acid mixture, the test animals exhibited rapid and nearly complete (>95%) small intestinal absorption of test material, extensive conversion of over 90% of absorbed material to phospholipids and triglycerides (primarily in the liver and enteric tissues) and widespread distribution of these conversion products throughout the body. While providing substrates for a number of pathways of fatty acid metabolism, ingested cetylated fatty acids do not appear to accumulate within either tissues or blood.[23]

The abilities of individual cetylated fatty acids to prevent adjuvant-induced joint arthritis has been studied in rodents.[24] In this model, pretreatment with either cetyl myristoleate or cetyl oleate significantly reduced the severity of joint swelling and loss of appetite otherwise produced by subsequent injection of adjuvant. In contrast, pretreatment with cetyl myristate was ineffective. In an alternative model, concurrent supplementation with

synthetic cetyl myristoleate (20 mg per kg bodyweight) was significantly more successful than placebo in reducing the incidence of any clinical signs of joint arthritis in mice that were injected subsequently with collagen.[25] Reduction in growth rate was not associated with exposure to exogenous cetylated fatty acids.

In humans with rheumatoid arthritis, dietary supplementation with oleate (6.8 g daily) for 24 weeks significantly inhibited ionophore-stimulated leukotriene B_4 (LTB_4) production and produced significantly improved physician evaluation of global condition.[26] However, the apparent improvement could not be attributed to any particular characteristic of any individual rheumatic joint but instead represented the net result of a combination of small individual improvements.

In a peer-reviewed published randomized placebo-controlled human clinical trial, patients with chronic osteoarthritis of the knee were assigned randomly to ingest either placebo capsules containing 3000 mg soy lecithin daily or test capsules of Celadrin™ providing 1554.5 mg of cetylated fatty acids (cetyl myristoleate 388.5 mg, cetyl myristate 621.5 mg, cetyl palmitoleate 109 mg, cetyl laurate 15.5 mg, cetyl palmitate 78 mg, cetyl oleate 311 mg, cetyl decanoate 15.5 mg and cetyl stearate 15.5 mg) plus 630 mg olive oil, 300 mg soy lecithin, 66 mg eicosapentaenoic acid and 54 mg of docosahexaenoic acid daily.[27-29] After 68 days (total cetylated fatty acid ingestion, 105,706 mg), patients consuming the test material exhibited a statistically and clinically significant increase of 10 degrees in average range of motion of affected knees (compared to 2 degrees of improvement in subjects consuming placebo; $p < 0.01$) and significant increases in several measures of functional independence. In addition, 58% of patients receiving the test material reported a reduction in joint pain, compared to 32% of those receiving placebo (relative risk for no pain reduction, test material vs. placebo: 0.63; 95% CI: 0.39-1.00). There was no significant treatment-related difference in the degree of joint swelling, suggesting the cetylated fatty acids act to enhance the balance between degradation and replacement of matrix molecules rather than by effects on inflammatory processes. At the same time, pain in human osteoarthritis is thought to be related to the degree of inflammation present and pharmacologic pain reduction that is accompanied by a reduction in the severity of inflammation also has been found to be associated with reduction in the severity of matrix molecule degradation.[30] Although no adverse events were reported, no data concerning liver function, kidney function, biomarkers of cardiovascular health or hematologic characteristics were presented. Reduction in growth rate was not associated with exposure to exogenous cetylated fatty acids.

The findings of these investigators support the conclusion that daily supplementation with dietary supplements containing a mixture of cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laurate, cetyl palmitate and cetyl oleate increases the range of motion of osteoarthritic joints and increases functional independence.[27-29] They also suggest that daily dietary supplementation with such products reduces pain in affected joints.[27-30] Dietary supplementation with such mixtures of cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laurate, cetyl palmitate and cetyl oleate can exert the effects described above only through the stimulation of beneficial responses within joint cartilage through

which the restoration and maintenance of the structural and biochemical integrity of the cartilage are fostered. Because the phenomena of degenerative change within articular cartilage are characterized by a continuum of severity that ranges from early strictly biochemical change in asymptomatic and otherwise apparently healthy joints to severely degenerate articular cartilage in painful joints, without alteration in the ability of chondrocytes within the range of affected tissue to respond to stimuli, the findings concerning daily dietary supplementation with oral Celadrin™ also support the conclusion that the cetylated fatty acid ingredients of oral Celadrin™ contribute to the maintenance of the structural and biochemical integrity of articular cartilage without affecting body weight.[27-29]

In a series of Ames tests utilizing the bacterial reverse mutation assay applied to several stains of *Salmonella typhimurium*, no mutagenic effects were associated with exposure to Celadrin™.[31] In a study of the acute toxicity of oral Celadrin™, mice were given an oral bolus containing 31.5 g of Celadrin™ per kg bodyweight (about 1300 times the recommended daily human intake of approximately 22.5 mg per kg bodyweight).[32] There were no acute or subacute responses to the test material. At slaughter seven days after dosing, test animals exhibited no signs of gross pathology, histopathology or reduced rates of weight gain. Oral Celadrin™ appears to have no acutely toxic effects when ingested in such large amounts.

Conclusions

- The provision of a supplemental mixture of cetylated fatty acids (orally or topically) contributes to the preservation of the biochemical and mechanical integrity of articular cartilage, inhibits the initiation of degenerative osteoarthritic change in articular cartilage and inhibits the progression of degenerative osteoarthritic change to overt cartilage deterioration, inhibits the progression of overt cartilage deterioration to joint degeneration, and inhibits the progression of joint degeneration in symptomatic osteoarthritis.[27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ supports comfortable joint movement.[27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ supports healthy joint flexibility.[27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ supports the maintenance of joint flexibility.[27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ provides support for healthy joint function.[27-29]

- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ supports the lubrication of joints. [27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ provides support for maintaining the cushioning properties of joints. [27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ provides support for joint mobility. [27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ supports joint health. [27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ maintains healthy joints. [27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ is safe. [27-29,31,32]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ has no effect on the β-oxidation of free fatty acids. [27-29]
- Daily dietary supplementation with 1554 mg of a mixture of cetylated fatty acids such as that found in Celadrin™ does not induce changes in body weight. [27-29]

Modified Cellulose-Based Polysaccharides of Plant Origin and Cetylated Fatty Acids in Combination and Weight Loss

In a double-blind, randomized, placebo-controlled trial of the effects of dietary supplementation with a combination of a mixture of modified cellulose-based polysaccharides of plant origin (700 mg with meals, three times daily) and cetylated fatty acids (50 mg with meals, three times daily) on overweight and obese adult women it was found that the addition of the supplemental blend to a weight loss regimen consisting of a calorie-restricted diet calculated to provide a 500 kcal daily energy deficit and a supervised cardiovascular exercise program (30 to 60 minutes of moderate exercise 4 or 5 times weekly) for 8 weeks produced a statistically significant average of 6 kg more weight loss than was produced by the weight loss program supplemented with placebo (a difference of 4 kg would be predicted by the above calculations, suggesting that the daily caloric deficit induced by the supplemental blend exceeded 400 kcal).[33] This greater amount of weight loss was accompanied by significantly greater reductions in total body fat, body mass index and waist circumference. No clinically significant adverse reactions were reported to have occurred during this study.

Conclusions

- Daily dietary supplementation with 2100 mg of a mixture of modified cellulose-based polysaccharides of plant origin induces fat loss in humans.[33]
- Dietary supplementation with a mixture of modified cellulose-based polysaccharides of plant origin induces weight loss in humans.[33]
- Daily dietary supplementation with 2100 mg of a mixture of modified cellulose-based polysaccharides of plant origin induces weight loss in humans.[33]
- Dietary supplementation with a mixture of modified cellulose-based polysaccharides of plant origin supports healthy body composition in humans.[33]
- Daily dietary supplementation with 2100 mg of a mixture of modified cellulose-based polysaccharides of plant origin supports healthy body composition in humans.[33]
- Daily dietary supplementation with 2100 mg of a mixture of modified cellulose-based polysaccharides of plant origin is safe.[8-17,19-21,33]
- Daily dietary supplementation with 150 mg of cetylated fatty acids does not increase the amount of additional weight loss induced by daily dietary supplementation with 2100 mg of a mixture of modified cellulose-based polysaccharides of plant origin.[19,27-29]
- Daily dietary supplementation with up to 1554 mg of a mixture of cetylated fatty acids does not induce changes in body weight.[27-29]

Modified Cellulose-Based Polysaccharides of Plant Origin and Endocrine Responses that are Consistent with Weight Loss

In human studies, dietary supplementation with a mixture of modified cellulose-based polysaccharides of plant origin produced an acceleration of body fat reduction that was accompanied by a significantly greater increase in average fasting serum adiponectin concentration[33] and with a significantly greater decrease in average fasting serum leptin concentration, compared to the responses to placebo.[18,33] The physiologic relationships among insulin resistance, adiponectin and leptin suggest that the additional weight loss associated with HPMC supplementation resulted from increased β-oxidation of free fatty acids. Human insulin resistance is associated with decreased efficiency of β-oxidation of free fatty acids[34-43] and with elevated fasting serum leptin concentrations,[44-49] depressed fasting serum adiponectin concentrations[45-47,50,51] and decreased adiponectin:leptin fasting serum concentration ratios.[48,52,53] In contrast, increasing adiponectin secretion

increases insulin sensitivity[54,55] and accelerates the β-oxidation of free fatty acids.[55] In addition, human weight loss is accompanied by increases in fasting serum adiponectin concentrations and decreases in fasting serum leptin concentrations that are proportional to the extent of weight loss.[45,56-59] These physiologic relationships could explain, at least in part, the weight loss-accelerating effect of dietary supplementation with a mixture of modified cellulose-based polysaccharides of plant origin.[18,33]

The results of an unpublished study of rats are consistent with these conclusions.[60] Growing rats fed a "polysaccharides tri-blend" form of HPMC for 6 weeks exhibited a significant shift in growth from body fat to lean body mass, compared to pair-fed littermates. In addition, less fat accumulated in their livers, fasting serum lepin and resistin concentrations were reduced significantly more, and transient postprandial excursions of serum leptin concentrations were significantly smaller. By analogy with the human data cited above,[19,45,56-59] and the additional report that decreasing fasting serum resistin concentration reflects increased insulin sensitivity and normalization of fasting glycemia,[54] these results all are consistent with HPMC-induced acceleration of the β-oxidation of free fatty acids. Additional evidence supporting this conclusion is provided by the HPMC-supplemented rats, which exhibited significantly greater expression of carnitine palmitoyl transferase 1B (CPT1; reflecting increased β-oxidation of free fatty acids[61]), significantly greater expression of uncoupling protein-3 (UCP-3; reflecting increased β-oxidation of free fatty acids[62]), and significantly lower expression of malonyl-CoA decarboxylase (MCD; reflecting decreased inhibition of CPT1 by MCD resulting in increased β-oxidation of free fatty acids[61]).

Conclusions

- Dietary supplementation with a mixture of modified cellulose-based polysaccharides of plant origin is associated with several endocrine changes that are consistent with acceleration of the β-oxidation of free fatty acids.[18,33-62]

This report represents the credible and reliable published scientific evidence available on November 3, 2011. The conclusions drawn may differ from those that may be drawn by another reviewer evaluating the same evidence or from those that may be drawn by a representative of a governmental agency. They are based on the published English-language scientific evidence available on November 3, 2011, and may or may not be supported by scientific evidence presented or published after that date. The conclusions drawn are presented for illustrative purposes only and are not intended for use in the formulation, labeling or promotion of any products. Before those statements or any similar statements derived from them are used in the formulation, labeling or promotion of any products, they should first be submitted to review by an attorney trained and experienced in regulatory affairs regarding the formulation, labeling and promotion of dietary supplements. These conclusions and statements are not applicable to any product intended to or implied to be able to diagnose, treat, cure or prevent any disease.

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