(54) Title: TAGATOSE AS A NOVEL TREATMENT FOR METABOLIC SYNDROME X, DYSLIPIDEMIA, AND CORONARY ARTERY DISEASE

(57) Abstract: The administration of tagatose (D-tagatose, L-tagatose, or a combination of the two isomers) to animals, including humans, to treat metabolic syndrome X, dyslipidemia and coronary artery disease is provided. The administration of tagatose (D-tagatose, L-tagatose, or a combination of the two isomers) to animals, including humans, reduce the risk for heart attacks, coronary artery disease, and restenosis after angioplasty is also provided. Tagatose improves cardiovascular health and treats cardiovascular disease by increasing HDL-cholesterol levels. Tagatose treats metabolic syndrome X by reducing the animals weight and dyslipidemia, and improving glucose intolerance.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
Tagatose as a Novel Treatment for Metabolic Syndrome X, Dyslipidemia, and Coronary Artery Disease

Background of the Invention

Field of the Invention

[01] This invention relates to the use of tagatose for the treatment of dyslipidemia, coronary artery disease, and metabolic syndrome X and for reducing the risk for heart attacks and restenosis after angioplasty.

Related Art

[02] Insulin resistance is defined as a decreased sensitivity in the peripheral tissues to a biological amount of insulin and was recognized as an important component of Type 2 diabetes mellitus over 50 years ago (Himsworth HP; Diabetes mellitus: Its differentiation into insulin sensitive and insulin insensitive types, *Lancet*, 1:127-130 (1936)). The development of the euglycemic clamp technique (DeFronzo RA, et al.; Glucose clamp technique: A method for quantifying insulin secretion and resistance, *Am. J. Physiol.*, 237:E214-E223 (1979)) allows for the estimation of peripheral insulin-stimulated glucose uptake and the degree of insulin resistance present primarily in muscle. This technique has contributed evidence that peripheral insulin resistance is a primary factor in the development of Type 2 diabetes mellitus (DeFronzo R, et al.; Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease, *Diabetes Care*, 14:173-194 (1991); Lillioja S, et al.; Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians, *N. Engl. J. Med.*, 329:1988-92 (1993); Kahn CR; Banting Lecture: Insulin action, diabetogenes, and the cause of type II diabetes, *Diabetes*, 43:1066-84 (1994)). More recently, a WHO Expert Committee defined insulin resistance as present when insulin sensitivity, as measured under euglycemic hyperinsulinemic conditions, falls below the lowest quartile for the population under investigation (Beck-Nielsen H; General characteristics of the insulin
resistance syndrome: prevalence and heritability: European Group for the Study of Insulin Resistance (EGIR), *Drugs*, 58:7-10; discussion 75-82 (1999)).

[03] Decreased insulin-stimulated glucose uptake is now known to be a major component in the metabolic syndrome X, generally defined as a cluster of disorders including central obesity, glucose intolerance, hyperinsulinemia, dyslipidemia, and hypertension. Over 50 years ago, Vague proposed that central obesity increased the predisposition for these diseases, including diabetes mellitus and atherosclerosis (Vague J; The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease, *Am. J. Clin. Nutr.*, 4:20-34 (1956)). Some years later, Reaven (Reaven G; Banting lecture 1988: Role of insulin resistance in human disease, *Diabetes*, 30:1595-1607 (1988)) proposed the term Syndrome X for the clustering of glucose intolerance, hyperinsulinemia, dyslipidemia, and hypertension, and in addition, he suggested that insulin resistance is a unifying factor underlying these disorders.

[04] In addition to high LDL-cholesterol and triglyceride levels being associated with an increase risk for coronary artery disease and heart attacks, low HDL-cholesterol level is also associated with coronary artery disease (CAD) and heart attacks. The Framingham Heart Study showed low HDL levels to be an independent risk factor for CAD. Specifically, there is a 10% increase in CAD for each 4 mg/dL decrease in HDL (Castelli WP, et al., Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study, *JAMA*, 256(20):2835-8 (1986)). In addition, angiographic studies have shown a correlation between low HDL cholesterol levels and an increased number of diseased coronary arteries. Low HDL values were associated with an increased incidence of both triple-vessel disease and left main artery disease. One study found a fourfold increase in the rate of restenosis after angioplasty in patients with low HDL cholesterol levels (Shah PK, Amin J., Low high density lipoprotein level is associated with increased restenosis rate after coronary angioplasty, *Circulation*, 85(4):1279-85 (1992)). Thus, agents that increase HDL-cholesterol levels are useful for reducing CAD, risk of heart attacks and restenosis after angioplasty, and overall improvement of cardiovascular health.
D-tagatose is a ketohexose sweetener which has many uses. Some examples of its uses are as follows: a treatment for hemophilia and anemia (U.S. Patent 6,015,793 Levin); to increase fertility in women and improve fetal development (U.S. Patent 6,225,452 Levin); to treat diabetes mellitus (U.S. Patent 5,447,917 Zehner et al.); to slow aging (U.S. Patent 5,356,879, Zehner et al.); and as a weight loss agent (U.S. Patent 5,468,734, Seri et al.).


The long-term metabolic effects of D-tagatose in humans are unknown. In a 90 day study in rats, D-tagatose given as 15-20% of daily caloric intake led to less weight gain when compared to a control diet (Kruger CL, et al., 90-day oral toxicity study of D-tagatose in rats, *Reg. Tox. Pharm.*, 29:S1-10 (1999)).

But, D-tagatose and its isomer, L-tagatose, has not been reported to have any beneficial cardiovascular effects. Such beneficial cardiovascular effects include, but are not limited to, an increase in HDL-cholesterol levels, an increase in HDL-cholesterol levels along with a concurrent a reduction in LDL-cholesterol and triglyceride levels, a reduction in the risk for heart attacks, a reduction in the level of and risk for coronary artery disease, and a reduction in the risk for restenosis after angioplasty. In fact, in an eight week study, administration of 75 g of D-tagatose daily had no effect on blood cholesterol and lipid levels (Saunders JP, et al., Effects of

Furthermore, with the increase in the knowledge of metabolic syndrome X, nobody has reported that D-tagatose nor L-tagatose could be used as a treatment for this syndrome.

**Brief Description of the Invention**

[10] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to animals to increase HDL-cholesterol level in the blood of the animal. It is a further object that tagatose be administered to a mammal, including a human, to increase the level of HDL-cholesterol in the blood of that mammal, including a human.

[11] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to animals to decrease the level of LDL-cholesterol in the blood of an animal. It is a further object that tagatose be administered to a mammal, including a human, to decrease the level of LDL-cholesterol in the blood of that mammal, including a human.

[12] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to animals to decrease the level of triglycerides in the blood of an animal. It is a further object that tagatose be administered to a mammal, including a human, to decrease the level of triglycerides in the blood of that mammal, including a human.

[13] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to an animal to treat metabolic syndrome X in an animal in need of treatment thereof. It is a further object that tagatose be administered to a mammal, including a human, to treat metabolic syndrome X by reducing the animal’s weight and dyslipidemia, and improving glucose intolerance.

[14] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to an animal to reduce the risk for coronary artery disease. It is a further object that tagatose be administered to a mammal, including a human, to reduce the risk for coronary artery disease in that mammal, including a
human. It is also an object of this invention that the reduction in risk for coronary artery disease results from an increase in the HDL-cholesterol levels in the blood of the mammal, including human, by administration of tagatose.

[15] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to an animal to reduce the risk for restenosis after angioplasty. It is a further object that tagatose be administered to a mammal, including a human, to reduce the risk for restenosis after angioplasty. It is also an object of this invention that the reduction of risk for restenosis after angioplasty results from an increase in the HDL-cholesterol levels in the blood of the mammal, including human, by administration of tagatose.

[16] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to an animal to reduce the risk for heart attacks. It is a further object that tagatose be administered to a mammal, including a human, to reduce the risk for heart attacks in that mammal, including a human. It is also an object of this invention that the reduction in risk for heart attacks results from an increase in the HDL-cholesterol levels in the blood of the mammal, including human, by administration of tagatose.

[17] It is an object of this invention to administer tagatose (D-tagatose, L-tagatose, or a combination of both isomers) to an animal to improve the cardiovascular health of that animal. It is a further object that tagatose be administered to a mammal, including a human, to improve the cardiovascular health in that mammal, including a human. It is also an object of this invention that the improvement of cardiovascular health results from an increase in the HDL-cholesterol levels in the blood of the mammal, including human, by administration of tagatose.

**Brief Description of the Figures**

[18] Figure 1 illustrates the percentage of glycosylated hemoglobin in the subjects (♦ for N=8; ■ for N=5) taking D-tagatose.

[19] Figure 2 shows HDL-cholesterol levels in the subjects (♦ for N=8; ■ for N=6) taking D-tagatose.
Figure 3 shows the weight change in subjects (♦ for N=8; □ for N=5) taking D-tagatose.

**Detailed Description of the Invention**

This invention involves the treatment of an animal, including human, having metabolic syndrome X by the administration of an effective amount of tagatose, *i.e.*, D-tagatose, L-tagatose, or a mixture of the two isomers.

This invention also involves the method for reducing the blood levels of LDL-cholesterol and/or for increasing the blood levels of HDL-cholesterol of an animal, including human, by the administration of an effective amount of tagatose, *i.e.*, D-tagatose, L-tagatose, or a mixture of the two isomers.

This invention also involves the method for reducing the risk for coronary artery disease in an animal, including human, by the administration of an effective amount of tagatose, *i.e.*, D-tagatose, L-tagatose, or a mixture of the two isomers.

This invention also involves the method for reducing the risk for heart attack in an animal, including human, by the administration of an effective amount of tagatose, *i.e.*, D-tagatose, L-tagatose, or a mixture of the two isomers.

This invention also involves the method for reducing the risk for restenosis after angioplasty in an animal, including human, by the administration of an effective amount of tagatose, *i.e.*, D-tagatose, L-tagatose, or a mixture of the two isomers.

The tagatose may be administered to an animal, including human, in combination with a food or beverage, or taken separately in power, crystalline, or liquid form. As diluent, if needed, one may use liquid or solid carriers such as water, starch, alcohol, or other non-toxic substances. Preferably, the tagatose (D-tagatose, L-tagatose, or a combination of D-tagatose and L-tagatose) is administered in the weight range of 100 mg/kg body weight/day to 2,000 mg/kg body weight/day. The tagatose may be administered daily, every other day, or at other prescribed frequencies. Furthermore, the daily dosage may be administered once, twice, three times or more per day. It may be administered in combination with other medications known to be suitable for use in the treatment of metabolic X syndrome,
cardiovascular diseases, coronary artery disease, and dyslipidemia, or for medication to reduce LDL-cholesterol levels, or for the prevention of restenosis after angioplasty.

[27] Twelve subjects (6 male and 6 female) with type 2 DM for at least one year duration were enrolled and ranged from 35 to 70 years in age. Data analysis was performed on the eight subjects (4 male and 4 female) who completed all fourteen months of the study. Four subjects discontinued the study soon after D-tagatose therapy was initiated and were not included in data analyses. Two subjects withdrew during the first week of D-tagatose because of persistent gastrointestinal symptoms including diarrhea, flatulence, and/or bloating. One subject with asthma withdrew after two months of daily D-tagatose because of a persistent, dry cough. The cough resolved after discontinuation of the D-tagatose and appeared to recur after re-initiation of the D-tagatose, which led the subject to withdraw from the study. The fourth subject withdrew after moving to another state.

[28] At entry, three subjects were receiving diet therapy alone, four subjects were being treated with a sulfonylurea, and one subject was being treated with combination metformin and troglitazone. Those subjects receiving medications had been on stable doses for at least ten months prior to enrollment. Three subjects had oral diabetes medications added or adjusted by their primary care providers during the treatment phase of the study. One subject had glipizide 5 mg added at month 3.75 and another subject had her glyburide dosage increased at month 7.5 of the treatment phase. The third subject had glyburide 2.5 mg added at month 2.25 and had her troglitazone dose increased from 200 mg to 400 mg daily at month 4 of the treatment phase. These three subjects were included in all outcome analyses, though subgroup analyses were done for glycosylated hemoglobin (GlyHb) and body weight parameters which are known to be affected by sulfonylureas and troglitazone. One subject had pravastatin added at month 7.3. A lipid subgroup analysis was performed which excluded this subject and the one whose troglitazone was increased during the study. A subgroup analysis was also performed on three subjects who had anti-hypertensive medications added during this study.
Subjects were excluded from study entry if baseline GlyHb levels were <8% (normal range 4.4% -- 7.7%) or if they had gastrointestinal disorders. All investigational protocols were approved by the Institutional Review Board of the University of Maryland, Baltimore, and participants were enrolled only after giving written informed consent.

D-tagatose was prepared by Biospherics Incorporated (Beltsville, Maryland). Samples provided to subjects were >99% pure by HPLC analysis and were weighed and packaged in the University of Maryland, Baltimore Pharmacy School prior to administration.

Study Protocol

After a two month run-in period, subjects were given 15 g packages of D-tagatose to be taken three times daily with meals for a total of 45 g per day. With an median weight of approximately 100 kg, each subject took approximately 450 mg/kg/day. Dose-dependent, gastrointestinal side effects observed with large doses of D-tagatose have been attributed to an osmotic effect of this poorly absorbed sugar. Prior tolerance testing at the University of Maryland, Baltimore, has shown the 15 g dosage to be typically well-tolerated with minimal adverse gastrointestinal effects (Donner TW, et. al.; Diab. Obes. & Metab., 1:285-292 (1999)).

The D-tagatose was dissolved in liquids, used in baking, or added to prepared foods. D-tagatose compliance was assessed at each visit by package count. For the duration of the fourteen month study period, subjects were encouraged not to otherwise alter their dietary intake. All subjects enrolled were physically inactive and remained so throughout the fourteen month observation period.

At the initial visit and every two months for the next fourteen months, body weight and vital signs were recorded, and fasting blood was tested for glucose, GlyHb, insulin, lipids, liver and kidney function, uric acid, bilirubin, phosphorus, calcium, magnesium, bicarbonate, chloride, sodium, potassium, total protein, albumin, and amylase. Subjects were questioned at each visit about the occurrence of any adverse events or side effects, and specifically about any gastrointestinal side effects.
Statistical Analysis

[34] Mean values of each physiologic measurement were calculated at each follow-up time. To assess whether there was a statistically significant trend in the means over time, we fit mixed effects regression models including a random slope and random intercept for each study subject (Laird NM, et al.; Random-effects models for longitudinal data, *Biometrics*, 38:963-974 (1982)). These models were fit using the “lme” software library for the R system for statistical computation and graphics.

[35] Three subjects had new medications added or medication dosages adjusted during follow-up that might have had an impact on their weight, GlyHb, or cholesterol. To avoid the potential confounding effects of these changes, the observations from these subjects which occurred after the start of the new medications for some of the analyses were not included.

[36] Data are presented as means +/- standard deviation. Associates with a p-value <0.05 are referred to as statistically significant. Baseline means were calculated by averaging both pretreatment means.

Laboratory evaluations

[37] Glycosylated hemoglobin (GlyHb) values were measured by the affinity column method (Helena Glyco-Tek, Beaumont, Texas) using well-known in the artfield techniques, which has a normal range of 4.4% -- 7.7% and a mean intra-assay coefficient of variation of 2.95%. Insulin levels were measured by the Coates-Account radioimmunoassay (RIA) method (Diagnostic Products Corporation, Los Angeles, California). Chemistry profiles and lipids were performed at the University of Maryland, Baltimore Chemistry Laboratory using well-known in the art field techniques.

Results

[38] Eight subjects completed the full fourteen months of the study protocol and were included in the efficacy analyses. Of these eight subjects, four were male and four were female with a mean age of 50.7 years. At baseline, study subjects were obese with a mean body mass index (BMI) of 36.7 kg/m², and in poor glycemic control with a mean GlyHb of 11.2% (NI, 4.4% -- 7.7%). Subjects were also
dyslipidemic at baseline with a mean total cholesterol level of 228 mg/dl, LDL-cholesterol level of 146 mg/dl, triglycerides levels of 226 mg/dl, and HDL-cholesterol level of 31 mg/dl.

[39] During the two month run-in period, modest increases were observed for both mean body weight (+0.5 kg) and GlyHb (+1.1%). Thereafter, body weight and GlyHb remained stable for the first four months of D-tagatose therapy, and then progressively declined (Figures 1 and 2). Seven of the eight subjects lost weight during the treatment phase with a mean fall from 109 +/- 14/7 kg at baseline to 105.3 +/- 14.4 kg at month twelve (p=0.01, test for trend). The single subject who gained weight during the treatment period had been started on a sulfonylurea and had his triglitazone increased during the study. When this subject and two others who had a sulfonylurea added or dosage increased during the study were excluded from data analysis, a more substantial weight loss of 5.1 kg over the twelve month intervention period was observed (Figure 1, p=0.001, test for trend).

[40] After twelve months of D-tagatose, a significant decrease in GlyHb was observed in the eight subjects who completed the study, with levels dropping from 11.2 +/- 2.0% to 9.5 +/- 2.0% (Figure 2, p=0.02, test for trend). After the three subjects in whom hypoglycemic medications were added or increased during the study were excluded from analysis, a 1% decrease in GlyHb was still observed (10.6 +/- 1.9% v 9.6 +/- 2.3%). No changes were observed for fasting glucose or insulin levels during the treatment phase.

[41] Unexpectedly, an increase in HDL-cholesterol levels occurred throughout the twelve month intervention period in all eight subjects (Figure 3). Mean baseline HDL-cholesterol rose from 31.1 +/- 13.9 mg/dl to 40.5 +/- 10.4 mg/dl at month twelve (p=0.01). After the subjects in whom pravastatin was added (n=1) or whose troglitazone dose was increased (n=1) were excluded from data analysis, an even greater rise in HDL-cholesterol was seen, from 30.5 +/- 15.8 mg/dl to 41.7 +/- 12.1 mg/dl (p<0.001). No significant changes were observed in total cholesterol, LDL-cholesterol, or triglycerides during the study period. Additionally, no significant changes were observed in blood pressure during the twelve month intervention
period. Three subjects had cardiovascular medications added during the study, two
for hypertension (amlodipine and hydrochlorothiazide), and one who was
normotensive but post-myocardial infarction (metoprolol). No significant changes in
blood pressure were observed during the study when these three subjects were
excluded from analysis.

[42] D-tagatose was not found to have toxic effects on renal or hepatic functions,
measures of which did not change during the twelve month treatment period. No
other changes were observed in any of the other biochemical parameters tested during
the treatment period.

[43] Compliance with D-tagatose was confirmed in all eight subjects who
completed twelve months of D-tagatose based on package counts performed every
two months. During the first two weeks of D-tagatose therapy, gastrointestinal
symptoms were reported in all eight subjects. These symptoms were typically mild,
transient and included flatulence (n=6), diarrhea (n=4), and/or nausea (n=1).
Thereafter, adverse gastrointestinal effects resolved when the D-tagatose was taken as
directed, with the exception of a single subject who reported persistent, mild
flatulence through the first six months of the therapy. Three subjects, including the
one who was on metformin throughout the study, reported bloating, flatulence, and/or
diarrhea if more than 15 g of D-tagatose was consumed at a time or if the doses were
spaced less than three hours apart. A single subject with chronic constipation noted
more regular bowel habits throughout the twelve month treatment period.

[44] A 48 year-old man who had suffered a cerebrovascular accident four years
prior to the study entry suffered an uncomplicated myocardial infarction 4.5 months
into the treatment phase of the study. D-tagatose was not felt to play a role in his
myocardial infarction given numerous cardiovascular risk factors prior to study entry
including low HDL-cholesterol levels, high triglycerides and LDL-cholesterol levels,
mild diastolic hypertension, and his prior cerebrovascular accident. He was allowed
to continue with the study after missing D-tagatose for one week while hospitalized,
but was excluded thereafter from analyses for lipids and blood pressure because
metoprolol and pravastatin were added to his drug regimen following his myocardial infarction.

[45] Table 1 summarizes the information obtained during the course of this study. In Table 1, baseline values are the average of readings taken two months before and immediately before the treatment period.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Month 2</th>
<th>Month 4</th>
<th>Month 6</th>
<th>Month 8</th>
<th>Month 10</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>109.0 (8)</td>
<td>0.2 (8)</td>
<td>-0.1 (6)</td>
<td>-2.7 (6)</td>
<td>-3.3 (5)</td>
<td>-5.0 (5)</td>
<td>-5.1 (5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36.7 (8)</td>
<td>0.1 (8)</td>
<td>0.0 (6)</td>
<td>-0.9 (6)</td>
<td>-1.1 (5)</td>
<td>-1.7 (5)</td>
<td>-1.7 (5)</td>
</tr>
<tr>
<td>GlyHb (%)</td>
<td>11.2 (8)</td>
<td>0.5 (8)</td>
<td>1.2 (6)</td>
<td>0.8 (6)</td>
<td>-1.2 (5)</td>
<td>-1.2 (5)</td>
<td>-1.0 (5)</td>
</tr>
<tr>
<td>Fasting BG (mg/dl)</td>
<td>192 (8)</td>
<td>2 (8)</td>
<td>21 (6)</td>
<td>-2 (6)</td>
<td>-19 (5)</td>
<td>8 (5)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Fasting insulin (uu/ml)</td>
<td>24.7 (8)</td>
<td>10.2 (8)</td>
<td>1.9 (6)</td>
<td>4.0 (6)</td>
<td>-5.5 (5)</td>
<td>8.7 (5)</td>
<td>-1.3 (5)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>218 (8)</td>
<td>4 (8)</td>
<td>3 (8)</td>
<td>-12 (7)</td>
<td>25 (6)</td>
<td>22 (6)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>LDL (mg/dl)**</td>
<td>146 (8)</td>
<td>-2 (7)</td>
<td>-41 (7)</td>
<td>-13 (6)</td>
<td>-11 (5)</td>
<td>-8 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>30.4 (8)</td>
<td>1.6 (8)</td>
<td>1.4 (7)</td>
<td>3.6 (7)</td>
<td>6.4 (6)</td>
<td>6.1 (6)</td>
<td>12.1 (6)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>226 (8)</td>
<td>-9 (8)</td>
<td>80 (8)</td>
<td>9 (7)</td>
<td>75 (6)</td>
<td>225 (6)</td>
<td>24 (6)</td>
</tr>
</tbody>
</table>

* ( ) = number of subjects
** LDL cholesterol could not be calculated for one subject after baseline because triglyceride levels were > 400 mg/dl.

[46] This study is the first to investigate the long-term effects of D-tagatose in humans with type 2 DM. While the study population was small in size, significant and beneficial changes were seen in weight and HDL-cholesterol at the end of the twelve month intervention period. A 1% decline in GlyHb was also observed though this change was not significant once subjects were excluded who had been placed on oral diabetes medications during this study.

[47] The weight loss seen in the subjects occurred while glycemic control improved. Weight loss occurred in one subject in whom a sulfonylurea had been
added and in another whose sulfonylurea dosage had been increased. Indeed, the only subject who gained weight during the study did so only after being started on a sulfonylurea and having his thiazolidinedione dosage increased, two medications known to be associated with weight gain. When the five subjects who did not have changes in oral diabetes medications made during the study were evaluated, the mean weight loss observed following twelve months of D-tagatose was even greater (5.1 +/- 3.1 v 3.7 +/- 3.4 kg for all eight subjects).

[48] The etiology of weight loss that began after four months of D-tagatose in the study population is unclear. Subjects participating in the study did not change their dietary habits other than using D-tagatose as their sweetener. The eight subjects were sedentary and did not modify their physical activity during the study.

[49] A progressive and marked rise in HDL-cholesterol was observed following dietary supplementation with D-tagatose. The low baseline HDL-cholesterol in the study population is seen commonly in obese patients with type 2 DM and has been shown to be a major risk factor for coronary heart disease (CHD) (Barter PJ, et al.; High density lipoproteins and coronary heart disease, Atherosclerosis, 121:1-12 (1996); Castelli WP, et al.; Incidence of coronary heart disease and lipoprotein cholesterol levels, JAMA, 256:2835-2838 (1986); Jacobs DR, et al.; High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: The follow-up study of the Lipid Research Clinics Prevalence Study, Am. J. Epidemiol., 131:32-47 (1990); and NIH Consensus Conference: Triglyceride, high density lipoprotein, and coronary heart disease, JAMA, 269:505-510 (1993)). An aggregate analysis of four large epidemiologic studies indicated that for each 1 mg/dl increase in HDL-cholesterol, one would expect a 2% decrease in CHD risk in men, and a 3% CHD decrease risk in women (Gordon DJ, et al.; High density lipoprotein cholesterol and cardiovascular disease, Circulation, 79:8-15 (1989)). Without wishing to be bound to one particular theory, it is possible that the reduction in body weight contributed to the improvement in HDL-cholesterol in this study. Kaplan showed that caloric restriction for three months in obese patients with type 2 DM leading to a 3 kg weight loss was associated with a 5.5 mg/dl increase in HDL-
cholesterol (Kaplan RM, et al.; Prospective evaluation of HDL cholesterol changes after diet and physical conditioning programs for patients with type II diabetes mellitus, *Diabetes Care*, 8:343-348 (1985)). Wing found a more modest 2.5 mg/dl increase in HDL-cholesterol in obese type 2 DM patients only with weight loss exceeding 6.9 kg, after one year of caloric restriction and increases exercise (Wing RR, et al.; Long-term effects of modest weight loss in type II diabetes patients, *Arch. Intern. Med.*, 147:1749-1753 (1987)). The subjects did not change their amount of physical activity or alcohol intake, and none were smokers, all parameters which can affect HDL-cholesterol. Again not wishing to be bound to any one theory, it is not known if the extensive hepatic metabolism of D-tagatose is additionally influencing hepatic synthesis of HDL-cholesterol.

[50] Oral administration of D-tagatose has previously been shown to blunt hyperglycemia significantly following oral glucose in a dose-dependant manner in subjects with type 2 DM (Donner TW, et al.; *Diab. Obes. & Metab.*, 1:285-292 (1999)). Doses of D-tagatose as low as 10 g were efficacious. Subjects in this study received 15 g of D-tagatose with meals for 12 months. A number of limitations of this pilot study likely prevented a significant decline in GlyHb from being observed. First, the 1.1% increase in GlyHb which occurred during the two month run-in period demonstrates that study subjects were in a state of deteriorating glycemic control when they began D-tagatose therapy. A placebo-control DM population would have helped better quantitate this effect.

[51] Deteriorating diabetic control at study entry may help explain why a progressive decline in GlyHb was not seen until after the fourth month of D-tagatose therapy. The study was also limited by the small number of subjects who were enrolled and by the three subjects in whom medication adjustments by outside physicians led to subsequent GlyHb values being excluded from data analysis. There is no evidence in this study of a D-tagatose-associated deterioration of diabetic control. Of the three subjects who had oral diabetes medications added or dosages increased during the study, two subjects entered the study with very elevated GlyHb levels but had seen a reduction in GlyHb the two months prior to having medication
adjustments made. The third subject had 2.4% increase in GlyHb during the two month run-in period, and had a progressive deterioration in glycemic control for the next six months. Among the five subjects who received twelve months of D-tagatose and had no oral diabetes medications added during the study, a 1% decrease in GlyHb was seen. Stable fasting glucose and insulin levels were observed during the treatment period while GlyHb levels were falling. It is possible that D-tagatose was improving postprandial hyperglycemia, an effect seen when D-tagatose is administered prior to oral GTT (Donner TW, et al.; *Diab. Obes. & Metab.*, 1:285-292 (1999)). A larger, placebo-controlled study is needed to confirm whether D-tagatose use in type 2 DM patients improves glycemic control, and to what degree better glycemic control correlates with weight loss.

[52] Daily ingestion of tagatose with food leads to weight loss and increases in HDL-cholesterol in patients with type 2 diabetes. The rise in HDL-cholesterol is disproportionate to the degree of weight loss or improved glycemic control observed in the example contained herein. Such beneficial effects can help reduce cardiovascular disease in this high-risk population and as well as improve cardiovascular health in all animals.

[53] It is appreciated that details of the foregoing embodiments, given for purposes of illustration, are not to be construed as limiting the scope of this invention. Although only a few exemplary embodiments of this invention have been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention, which is defined in the following claims and all equivalents thereto. Further, it is recognized that many embodiments may be conceived that do not achieve all of the advantages of some embodiments, particularly of the preferred embodiments, yet the absence of a particular advantage shall not be construed to necessarily mean that such an embodiment is outside the scope of the present invention.
Claims

What is claims is:

1. A method for treating metabolic syndrome X in an animal comprising; administering an effective amount of tagatose to an animal in need of treatment thereof.

2. The method of Claim 1 wherein the animal is a mammal.

3. The method of Claim 1 wherein the animal is a human.

4. The method of Claim 1 wherein from 100 – 2,000 mg/kg body weight/day is administered to said animal.

5. The method of Claim 1 wherein said tagatose is comprised of D-tagatose, L-tagatose, or a mixture of D-tagatose and L-tagatose.

6. A method for increasing the blood level of HDL-cholesterol in an animal comprising administering an effective amount of tagatose to an animal.

7. The method of Claim 6 wherein the animal is a mammal.

8. The method of Claim 6 wherein the animal is a human.

9. The method of Claim 6 wherein from 100 – 2,000 mg/kg body weight/day is administered to said animal.

10. The method of Claim 6 wherein said tagatose is comprised of D-tagatose, L-tagatose, or a mixture of D-tagatose and L-tagatose.

11. A method for decreasing the blood level of LDL-cholesterol in an animal comprising:

administering an effective amount of tagatose to an animal.

12. The method of Claim 11 wherein the animal is a mammal.

13. The method of Claim 11 wherein the animal is a human.

14. The method of Claim 11 wherein from 100 – 2,000 mg/kg body weight/day is administered to said animal.

15. The method of Claim 11 wherein said tagatose is comprised of D-tagatose, L-tagatose, or a mixture of D-tagatose and L-tagatose.

16. A method for treating dyslipidemia in an animal comprising:
administering an effective amount of tagatose to an animal in need of treatment thereof.

17. The method of Claim 16 wherein the animal is a mammal.

18. The method of Claim 17 wherein the animal is a human.

19. The method of Claim 18 wherein from 100 - 2,000 mg/kg body weight/day is administered to said animal.

20. The method of Claim 19 wherein said tagatose is comprised of D-tagatose, L-tagatose, or a mixture of D-tagatose and L-tagatose.

21. A method for improving the cardiovascular health of an animal comprising:

administering an effective amount of tagatose to an animal.

22. The method of Claim 21 wherein the animal is a mammal.

23. The method of Claim 21 wherein the animal is a human.

24. The method of Claim 21 wherein from 100 - 2,000 mg/kg body weight/day is administered to said animal.

25. The method of Claim 21 wherein said tagatose is comprised of D-tagatose, L-tagatose, or a mixture of D-tagatose and L-tagatose.

26. The method of Claim 21 wherein said cardiovascular health is indicated by an increase in HDL-cholesterol blood levels or a decrease in LDL-cholesterol blood levels, or both.

27. A method for reducing the risk of restenosis after angioplasty in an animal comprising:

administering an effective amount of tagatose to an animal.

28. The method of Claim 27 wherein the animal is a mammal.

29. The method of Claim 27 wherein the animal is a human.

30. The method of Claim 27 wherein from 100 - 2,000 mg/kg body weight/day is administered to said animal.

31. The method of Claim 27 wherein said tagatose is comprised of D-tagatose, L-tagatose, or a mixture of D-tagatose and L-tagatose.
32. The method of Claim 27 wherein said administration of tagatose increases the blood level of HDL-cholesterol in said animal.

33. A method for reducing the risk of coronary artery disease in an animal comprising:

administering an effective amount of tagatose to an animal.

34. The method of Claim 33 wherein the animal is a mammal.

35. The method of Claim 33 wherein the animal is a human.

36. The method of Claim 33 wherein from 100 – 2,000 mg/kg body weight/day is administered to said animal.

37. The method of Claim 33 wherein said tagatose is comprised of D-tagatose, L-tagatose, or a mixture of D-tagatose and L-tagatose.

38. The method of Claim 33 wherein said administration of tagatose increases the blood level of HDL-cholesterol in said animal.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/70
US CL : 514/23

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/23, 25

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
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<td>Y</td>
<td>LAERKE et al. D-Tagatose has Low Small Intestinal Digestability but High Large Intestinal Fementability in Pigs1,2, 3. May 1999, Vol. 129, No. 5, pages 1002-1009.</td>
<td>11-38</td>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search
20 May 2002 (20.05.2002)

Date of mailing of the international search report
02 JUL 2002

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Form PCT/ISA/210 (second sheet) (July 1998)
INTERNATIONAL SEARCH REPORT

Continuation of B. FIELDS SEARCHED Item 3:
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