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(71) Applicant *(for all designated States except US)*: **RELIANT PHARMACEUTICALS, INC.** [—/US]; 110 Allen Road, Liberty Corner, NJ 07938 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BOBOTAS, George** [US/US]; C/o Reliant Pharmaceuticals, Inc., 110 Allen Road, Liberty Corner, NJ 07938 (US). **RONGEN, Roelof, M.L** [US/US]; C/o Reliant Pharmaceuticals, Inc., 110 Allen Road, Liberty Corner, NJ 07938 (US). **FAWZY, Abdel** [US/US]; C/o Reliant Pharmaceuticals, Inc., 110 Allen Road, Liberty Corner, NJ 07938 (US). **KLING, Douglas** [US/US]; C/o Reliant Pharmaceuticals, Inc., 110 Allen Road, Liberty Corner, NJ 07938 (US).

(74) Agents: **CONNELL, Michaele** et al.; Arent Fox LLP, 1050 Connecticut Avenue N.W., Washington, DC 20036 (US).

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(54) **Title:** CB1 ANTAGONIST AND A DYSLIPIDEMIC AGENT AND/OR METABOLIC REGULATOR, AND METHODS OF MAKING AND USING SAME

(57) **Abstract:** The present invention relates to a CB1 antagonist and a dyslipidemic agent and/or a metabolic regulator. The present invention further includes methods of using formulations of a CB1 antagonist and at least one of (a) omega-3 fatty acids, (b) MTP inhibitors, (c) DPP4 inhibitors, (d) sarsasapogenin, (e) smilagenin, (f) steroidal glycosides and/or (g) extracts of Artemisia spp. for treating various dyslipidemias; treating vascular disease; treating artherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; reducing the incidence of and/or delaying the onset of metabolic syndrome; and reducing the incidence of, and/or delay the onset of type II diabetes.

CB1 Antagonist and a Dyslipidemic Agent andlor Metabolic Regulator, and Methods of Making and Using Same

Background of the Invention

1. Field of the Invention

[0001] The present invention relates, generally, to compositions comprising a cannabinoid 1 (CB1) antagonist and a dyslipidemic agent and/or a metabolic regulator. Presently preferred dyslipidemic agents used in the compositions of the present invention may include, but are not limited to, omega-3 fatty acids, peroxisome proliferator-activated receptor (PPAR) agonists/antagonists, microsomal triglyceride transfer protein (MTP) inhibitors, and/or dipeptidyl peptidase-4 (DPP4) inhibitors. Presently preferred metabolic regulators used in the compositions of the present invention may include, but are not limited to, sarsasapogenin, smilagenin, steroidal glycosides and extracts thereof, and extracts of *Artemisia spp.* The present invention also includes pharmaceutical formulations made from the compositions, and methods of making such formulations. The present invention also includes methods of using formulations of a CB1 antagonist and at least one of (a) omega-3 fatty acids, (b) MTP inhibitors, (c) DPP4 inhibitors, (d) sarsasapogenin, (e) smilagenin, (f) steroidal glycosides and extracts thereof, and/or (g) extracts of *Artemisia spp.* for treating hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, artherosclerotic disease, and/or obesity; preventing and/or reducing cardiovascular and/or vascular events; reducing insulin resistance, fasting glucose levels, and/or postprandial glucose levels; and preventing and/or reducing the incidence of and/or delaying the onset of metabolic syndrome. The present invention further includes methods of using formulations of a CB1 antagonist and at least one of (a) omega-3 fatty acids, (b) MTP inhibitors, (c) DPP4 inhibitors, (d) PPAR agonists/antagonists, (e) sarsasapogenin, (f) smilagenin, (g) steroidal glycosides and extracts thereof, and/or (h) extracts of *Artemisia spp.* for preventing, reducing the incidence of, and/or delaying the onset of type II diabetes.

2. Description of the Related Art

[0002] Dyslipidemia is a general term used to describe various disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested in various ways, such as by elevation of total cholesterol, elevation of "bad" low-density lipoprotein cholesterol and/or triglyceride concentrations, and reduction in "good" high-density lipoprotein cholesterol concentrations. In humans, cholesterol and triglycerides are part of lipoprotein complexes in the bloodstream, and can be separated via ultracentrifugation into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) fractions. Cholesterol and triglycerides are synthesized in the liver, incorporated into VLDL, and released into the plasma.

[0003] Dyslipidemia is often associated with diabetes and high blood pressure, particularly in obese/overweight patients. The relationship can also be observed in pre-diabetic patients who exhibit “metabolic syndrome” or "Syndrome X," which is characterized by the presence of metabolic risk factors that may include 1) central obesity; 2) atherogenic dyslipidemia (blood fat disorders comprising mainly high triglycerides (“TG”) and low HDL-cholesterol (interchangeably referred to herein as “HDL”) that foster plaque buildups in artery walls); 3) raised blood pressure; 4) insulin resistance or glucose intolerance (the body can’t properly use insulin or blood sugar); 5) prothrombotic state (*e.g.*, high fibrinogen or plasminogen activator inhibitor in the blood); and 6) a proinflammatory state (*e.g.*, elevated high-sensitivity C-reactive protein in the blood). The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines define metabolic syndrome by the presence of three of the following five clinical parameters: a) a waist circumference greater than 102 cm for men, and greater than 88 cm for women; b) a triglyceride level greater than 150 mg/dl; c) an HDL-cholesterol less than 40 mg/dl for men, and less than 50 mg/dl for women; d) a blood pressure greater than or equal to 130/85 mmHG; and e) a fasting glucose greater than 110 mg/dl (or fasting glucose greater than 125 mg/dl, if 3 or more of the other criteria are present). Patients exhibiting the symptoms of metabolic syndrome are at increased

risk of coronary heart disease and other diseases related to plaque buildups in artery walls (*e.g.*, stroke and peripheral vascular disease). It is estimated that over 50 million Americans have metabolic syndrome.

[0004] The epidemics of obesity, type II diabetes, hypertension, and metabolic syndrome continue to worsen. These patients frequently do not respond to single-agent therapy, and many require combinations of drugs to address the various metabolic problems causing changes in their lipoprotein fractions. Although the need for combination therapy has been established in the management of hypertension and type II diabetes, it is less often used for the treatment of dyslipidemia. Most of the medications currently available for treating dyslipidemia fail to address the various additional conditions that are often associated therewith. It would therefore be desirable to provide compositions and methods for treating dyslipidemia, particularly in patients also suffering from obesity, type II diabetes, hypertension, and/or metabolic syndrome. There is a need in the art for compositions and methods for improving lipid profiles in patients suffering from obesity, type II diabetes, hypertension, and/or metabolic disorder.

[0005] Omega-3 fatty acids are known to reduce serum triglycerides by inhibiting diacylglycerol acyltransferase (DGAT) and by stimulating peroxisomal and mitochondrial beta oxidation. Marine oils, also commonly referred to as fish oils, are a good source of two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have been found to regulate lipid metabolism. Omega-3 fatty acids may include, but are not limited to, omega-3 polyunsaturated, long-chain fatty acids such as a eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid; esters of omega-3 fatty acids, optionally with glycerol, such as mono-, di- and triglycerides; and esters of the omega-3 fatty acids and a primary, secondary or tertiary alcohol such as fatty acid methyl esters and fatty acid ethyl esters. Omega-3 fatty acids or their esters, derivatives, conjugates, precursors, salts and mixtures thereof can be used either in their pure form or as a component of an oil such as fish oil, preferably

purified fish oil concentrates. Omega-3 fatty acids have been found to have beneficial effects on the risk factors for cardiovascular diseases, especially mild hypertension, hypertriglyceridemia and on the coagulation factor VII phospholipid complex activity. Omega-3 fatty acids lower serum triglycerides, increase serum HDL-cholesterol, lower systolic and diastolic blood pressure and the pulse rate, and lower the activity of the blood coagulation factor VII-phospholipid complex. Further, omega-3 fatty acids seem to be well-tolerated, without giving rise to any severe side effects.

[**0006**] One form of omega-3 fatty acid is a concentrate of omega-3, long chain, polyunsaturated fatty acids from fish oil containing DHA and EPA that is sold under the trademark LOVAZA™, which was formerly known as OMACOR®. Such a form of omega-3 fatty acid is described, for example, in U.S. Patent Nos. 5,502,077, 5,656,667 and 5,698,594, each of which is incorporated herein by reference.

[**0007**] Improving cholesterol and lipid levels is very important for long-term cardiovascular health, and is particularly important for reducing morbidity in patients who are also suffering from high blood pressure, type II diabetes, obesity, and/or metabolic syndrome. Various approaches have been taken to treat dyslipidemia.

[**0008**] U.S. Published Application No. 2005/0281868 describes a transdermal patch for combination therapy with a statin and another compound, for use in treating dyslipidemia. Exemplary transdermal products include any known statin that may be transdermally administered, in combination with various drugs, including rimonabant.

[**0009**] U.S. Published Application No. 2005/0171140 describes HMG CoA reductase inhibitors that may be useful for modulating blood serum lipids. These compounds may be combined with CB1 antagonists or inverse agonists, such as SR-141716 (Sanofi) and FLV-319 (Solvay).

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