Compositions Comprising 15-OHEPA and Methods of Using the Same

FIELD OF THE INVENTION

The invention pertains to the compositions, formulations and methods of treating fatty liver disorders (FLD), such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) and their sequelae by administration of a pharmaceutical composition comprising 15-hydroxy eicosapentaenoic acid (known as 15-OHEPA or 15-HEPE) in a subject in need thereof. In particular, the invention relates to a pharmaceutical composition with improved efficacy over one comprising EPA as the significant active component, rather than 15-OHEPA, for the treatment of subjects suffering from FLD and/or complications of FLD, to reduce fatty deposits in the liver to treat or prevent FLD and its associated complications.

SUMMARY

Fatty liver disorders, also known as fatty liver or fatty liver disease (FLD), relates to a condition where large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis, or abnormal retention of lipids within a cell. Despite having multiple causes, fatty liver is considered a single disease that occurs frequently in subjects with excessive alcohol intake and/or those who are obese (with or without effects of insulin resistance). The condition is also associated with other diseases that influence fat metabolism. FLD may be categorized into two separate conditions: alcoholic FLD and non-alcoholic FLD. Both conditions show micro-vesicular and macro-vesicular fatty changes at different stages of the disease. Accumulation of fat may also be accompanied by a progressive inflammation of the liver (hepatitis), called steatohepatitis. Fatty liver is also known in the art as alcoholic steatosis and non-alcoholic fatty liver disease (NAFLD), and the more severe forms as alcoholic steatohepatitis (part of alcoholic liver disease) and non-alcoholic steatohepatitis (NASH). Nonalcoholic fatty liver disease-associated cirrhosis is the most severe form of the disease and is characterized by liver inflammation that leads to scarring of the liver tissue, ultimately resulting in liver failure.

Obesity, metabolic syndrome, type 2 diabetes, and atherosclerosis are increasing at an alarming rate in the Western world. In recent years, fatty liver has emerged as an independent risk factor for these diseases. Fatty liver is the accumulation of triglycerides and other fats within hepatocytes. Fatty liver disease can range from fatty liver alone (also known as "steatosis"), to fatty liver associated with inflammation or steatohepatitis. Non-alcoholic fatty

liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are the most common causes of chronic liver disease in the adult population and represents a crucial risk factor for progression to liver failure, cirrhosis and hepatocellular carcinoma. While steatosis affects approximately 30% of the population, 80% of obese patients have NAFLD and 50% of patients undergoing bariatric surgery have steatohepatitis. NAFLD also represents the most common cause of liver disease in children. It is estimated that NAFLD affects up to 20 percent of adults and nearly 5 percent of children. Some experts estimate that about two thirds of obese adults and half of obese children may have fatty liver. In the past ten years, as the rates of obesity in have doubled in adults and tripled in children and teenagers, NAFLD and NASH are becoming more common. NASH can cause scarring and hardening of the liver, leading to cirrhosis, a very serious disease that may require a liver transplant, and eventually to hepatocellular carcinoma.

There is no single established medical treatment for fatty liver. Presently, treatment of NAFLD is limited to 1) treatment of associated metabolic disorders such as diabetes and hyperlipidemia; 2) the management of insulin resistance focusing on weight loss, exercise and/or a pharmacological approach; and 3) the use of antioxidants as hepatic protection agents. Despite the use of many different therapeutic modalities, no clear treatment is currently available to address NAFLD. Because it is clinically important to resolve NAFLD and its sequelae, new approaches aimed at preventing and reversing fat accumulation in the liver are necessary.

We have surprisingly found that 15-OHEPA, a metabolite of EPA, is more potent than EPA in the treatment of FLD. In one example, disclosed herein is the use of 15-OHEPA in the manufacture of a medicament for treating a fatty liver disorder. In one aspect, the present invention refers to use of 15-Hydroxy-eicosa-5,8,11,13,17-pentaenoic acid ("15-HEPE") in the manufacture of a medicament for treating a fatty liver disorder, wherein the 15-HEPE is in the form of its free acid, 15-hydroxyeicosa-5,8,11,13,17-pentaenoic acid, and/or a pharmaceutically acceptable ester thereof, or a mixture thereof. In one example, there is disclosed use of 15-Hydroxy-eicosa-5,8,11,13,17-pentaenoic acid or a pharmaceutically acceptable ester, derivative, conjugate, salt, or mixture thereof ("15-HEPE") 15-OHEPA in the manufacture of a medicament for treating a fatty liver disorder.

DETAILED DESCRIPTION

The present invention relates to compositions and methods for treating fatty liver disorders, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), by administration of a composition comprising 15-OHEPA in a subject in need thereof.

As used herein, "15-OHEPA" is 15-Hydroxy-eicosa-5,8,11,13,17-pentaenoic acid. 15-OHEPA can be synthesized from eicosapentaenoic acid, EPA according to methods known in the art. As used herein, the term "15-OHEPA" refers to 15-OHEPA in its free acid form (*e.g,* 15-hydroxy-eicosa-5,8,11,13,17-pentaenoic acid) and/or a pharmaceutically acceptable ester, conjugate or salt thereof, or mixtures of any of the foregoing. A derviative of 15-OHEPA may be used

Claims

1. Use of 15-Hydroxy-eicosa-5,8,11,13,17-pentaenoic acid ("15-HEPE") in the manufacture of a medicament for treating a fatty liver disorder, wherein the 15-HEPE is in the form of its free acid, 15-hydroxyeicosa-5,8,11,13,17-pentaenoic acid, and/or a pharmaceutically acceptable ester thereof, or a mixture thereof.

2. The use of 15-HEPE according to claim 1, in which the fatty liver disorder is selected from non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

3. The use of 15-HEPE according to claim 1 or claim 2, in which the 15-HEPE comprises a $C_1 - C_5$ alkyl ester.

4. The use of 15-HEPE according to any preceding claim, in which the 15-HEPE is in the form of a pharmaceutical composition.

5. The use of 15-HEPE according to claim 4, in which the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

6. The use of 15-HEPE according to claim 4 or claim 5, in which the pharmaceutical composition is an oral pharmaceutical composition.

7. The use of 15-HEPE according to any preceding claim, in which the 15-HEPE represents at least about 90%, by weight, of all fatty acids present.

8. The use of 15-HEPE according to any preceding claim, in which there are not more than 0.5% by weight of other fatty acids present.

9. The use of 15-HEPE according to any preceding claim, in which there is no other omega-3 fatty acid present.

10. The use of 15-HEPE according to any preceding claim, in which the 15-HEPE is present from about 50 mg to about 3000 mg.