

COMPOSITION FOR NORMALISATION OF FATTY LIVER AND METHOD FOR PRODUCING THE SAME

FIELD OF INVENTION

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This invention relates to a composition and method for producing the composition for oral administration to enhance the normalisation of fatty liver in mammals. More particularly, the composition is suitable for human being with liver problem, more particularly but not limited to non-alcoholic fatty liver disease (NAFLD).

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BACKGROUND OF THE INVENTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by increased fat accumulation as triglycerides in the liver and it is not caused by heavy alcohol use. According to Gastroenterology 1998; 114:842-5 and Hepatology, 2010; 52:1836-46, the *two-hits* and *multiple-hits* hypothesis proposed that the cause of NAFLD relates to obesity, diet and maternal predisposition. Patients with NAFLD and obesity have a relative deficit in energy expenditure and disturbances in lipid and glucose homeostasis due to excess macronutrient intake. These macronutrients such as sucrose and fructose can cause direct injury to the small intestinal wall epithelium. The disruption of small intestine integrity might affect the absorption and processing of vitamins. In view of the above, this invention provides a composition with effectively delivered micronutrients and vitamins to the liver and also facilitate hepatic regeneration thereof.

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SUMMARY OF INVENTION

One main aim of the present invention is to provide a drug delivery composition for normalising fatty liver using active ingredients comprising tocotrienols, tocopherols

and phospholipids.

At least one of the preceding aims is met, in whole or in part, by the present invention, in which one of the embodiments of the present invention is a drug delivery
5 composition of phospholipids, tocotrienols and tocopherols for oral administration to enhance the normalisation of fatty liver, wherein the amount of phospholipids in the composition is in the range of substantially 4.5 % (w/w) to substantially 20 % (w/w), the amount of the tocotrienols in the composition is in the range of substantially 10 % (w/w) to 35 % (w/w) and tocopherol in the composition is in the range of substantially
10 2 % (w/w) to substantially 10 % (w/w).

Preferably, the composition further comprises water-soluble vitamin selected from the group consisting of nicotinamide, cyanocobalamine and folic acid.

15 Preferably, the tocotrienols used comprises alpha tocotrienol in the range of substantially 3.5 % (w/w) to substantially 9 % (w/w) beta tocotrienol in the range of substantially 0.4 % (w/w) to substantially 2.2 % (w/w), gamma tocotrienol in the range of substantially 4.5 % (w/w) to substantially 15.5 % (w/w) and delta tocotrienol in the range of substantially 1 % (w/w) to substantially 7.5 % (w/w).

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Preferably, the tocopherol used comprises alpha tocopherol in the range of substantially 2 % (w/w) to substantially 10 % (w/w).

Preferably, the phospholipids used is plant-based phosphatidylcholine,
25 phosphatidylethanolamine, phosphatidic acid, phosphoinositides or phosphatidylserine.

Another aim of the present invention is to provide a composition which self-emulsify in the presence of aqueous medium with little agitation so as to improve

bioavailability of the active ingredients upon orally administered. More particularly, the composition aforementioned is further modified to obtain a self-emulsifying composition by adding suitable oil, surfactant and co-surfactant.

5 At least one of the preceding aims is met, in whole or in part, by the present invention, in which one of the embodiments of the present invention is a self-emulsifying composition for oral administration to enhance the normalisation of fatty liver, the self-emulsifying comprising a non-ionic surfactant, a co-surfactant, vegetable oil and active ingredients comprising phospholipids, tocotrienols and tocopherol.

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Preferably, the self-emulsifying composition further comprises water-soluble vitamins selected from the group consisting of nicotinamide, cyanocobalamine and folic acid.

Advantageously, the non-ionic surfactant used is polyoxy-35 castor oil.

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Advantageously, the co-surfactant used is caprylocaproyl macrogol-8-glycerides.

Advantageously, wherein the vegetable oil used is palm olein.

20 Another aim of the present invention is to provide a method for producing a composition comprising phospholipids, tocotrienols and tocopherol that self-emulsifies in the presence of aqueous medium. More particularly, the composition aforementioned is modified by the method so as to obtain the self-emulsifying composition.

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At least one of the preceding aims is met, in whole or in part, by the present invention, in which one of the embodiments of the present invention includes the use of a self-emulsifying composition comprising phospholipids, tocotrienols and tocopherols in the manufacturing of a supplement to enhance normalisation of fatty liver, wherein

the amount of phospholipids is in the range of substantially 4.5 % (w/w) to substantially 20 % (w/w), the amount of tocotrienols is in the range of substantially 10 % (w/w) to substantially 35 % (w/w) and the amount of tocopherols is in the range of substantially 2 % (w/w) to substantially 10 % (w/w).

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At least one of the preceding aims is met, in whole or in part, by the present invention, in which one of the embodiments of the present invention is a method for producing a self-emulsifying composition for oral administration to enhance the normalisation of fatty liver, the method comprising the steps of: mixing a non-ionic surfactant, a co-
10 surfactant and vegetable oil to obtain a first mixture; adding phospholipids into the first mixture and mixing to obtain a homogeneous second mixture; and adding tocotrienols and tocopherols into the second mixture and further mixing thereof until homogeneous.

15 Preferably, the method further comprises a step of melting beeswax into the vegetable oil, followed by adding there into the first mixture.

Preferably, the method further comprises a step of sieving water-soluble vitamin powder into the second mixture followed by shearing and milling thereof.

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DETAILED DESCRIPTION OF THE INVENTION

Exemplary, non-limiting embodiments of the invention will be disclosed. However, it is to be understood that limiting the description to the preferred embodiments of the
25 invention is merely to facilitate discussion of the present invention and it is envisioned that those skilled in the art may devise various modifications without departing from the scope of the appended claim.

The present invention provides a drug delivery composition of phospholipids

tocotrienols and tocopherols for oral administration to enhance the normalisation of fatty liver. Additionally, the composition comprises water-soluble vitamins therein to reduce hepatic cholesterol content of fatty liver. More particularly, the composition can be modified into a self-emulsifying composition by adding suitable oil, surfactant and co-surfactant. The self-emulsifying composition can form an emulsion easily with gentle agitation, such as movement of the stomach/intestine. As such, active ingredients in the composition can be absorbed efficiently in the body.

According to the embodiments of the invention, the applicant has found that, by combining or associating tocotrienols and tocopherols with phospholipids, a synergistic normalisation effect can be obtained which reduces the symptoms associated with diseases that are caused by excessive cellular oxidative activity and damaged hepatic membrane, more particularly of NAFLD. More particularly, the composition in the present invention enhances liver protective activity.

Accordingly, the present invention provides, in one embodiment, a composition comprising phospholipids, tocotrienols and tocopherols as the active ingredients in an edible capsule or the like. In some embodiments, water soluble vitamins can be further added as active ingredients therein to supplement liver health.

The tocotrienols and tocopherols used in the invention can be derived naturally or synthetically. They can be extracted from plants such as palm oil, rice bran oil, flaxseed oil, wheat germ, barley and certain types of nuts and grains but not limited thereto. It was found that the tocotrienols and tocopherols exhibits potent antioxidant activity in microsomal lipid peroxidation hence providing hepatoprotective property. More particularly, the tocotrienols used comprises alpha tocotrienol in the range of substantially 3.5 % (w/w) to substantially 9 % (w/w), beta tocotrienol in the range of substantially 0.4 % (w/w) to substantially 2 % (w/w), gamma tocotrienol in the range of substantially 4.5 % (w/w) to substantially 15.5 % (w/w), delta tocotrienol in the

range of substantially 1 % (w/w) to substantially 7.5 % (w/w). The tocopherol used comprises alpha tocopherol in the range of substantially 2 % (w/w) to substantially 10 % (w/w).

- 5 Another active ingredient used in the composition is phospholipids, more preferably plant-based phospholipids. Amongst others, the phospholipids used is phosphatidylcholine, phosphatidylethanolamine, phosphatidic acid, phosphoinositides or phosphatidylserine. In the preferred embodiments, the phospholipids used are derived from soy bean, such as soy bean lecithin. It was found that phospholipids can
- 10 be incorporated into damaged sections of membrane thereby facilitates hepatic regeneration and replaces endogenous, unsaturated phospholipids. Moreover, phospholipids can improve membrane fluidity and possess antioxidative, anti-inflammatory, apoptosis-modulating and anti-fibrotic properties.
- 15 In some embodiments, water-soluble vitamin selected from the group consisting of nicotinamide, cyanocobalamine and folic acid are used. Additional benefits from the water-soluble vitamin can enhance fatty liver normalisation effect of the composition in the present invention. It was found that nicotinamide can increase redox potential, reduce hepatic cholesterol content and substantially block the gain in liver weight.
- 20 Further, it was found that cyanocobalamine deficiency can induce higher rates of adiposity and accompanied by a change in lipid metabolism pathways. Supplementing cyanocobalamine can avoid the abovementioned changes. Moreover, folic acid can alleviate inflammatory response in liver thereby contribute to hepatoprotective effect.
- 25 The active ingredients can be formed into edible capsules which self-emulsify in the presence of aqueous medium with little agitation so as to improve bioavailability thereof upon orally administered. Particularly, the active ingredients can be blended with suitable oil, surfactant and co-surfactant. The present invention uses a combination of oil, surfactant and co-surfactant which enable the active ingredients to

be effectively released as well as absorbed by the body system. Particularly, palm olein is used as a carrier. Further, non-ionic surfactant is used due to its self-emulsifying capability. Further, the non-ionic surfactant used is non-toxic and non-reactive to produce a chemically stable system. Further, the co-surfactant used is
5 caprylocaproyl macrogol-8-glycerides. Together with the active ingredients aforementioned, the combination provides a stable emulsion upon slight agitation.

One embodiment of the present invention provides a self-emulsifying composition comprises substantially 0.5 % (w/w) to substantially 50 % (w/w) of palm olein,
10 substantially 1 % (w/w) to substantially 20 % (w/w) of caprylocaproyl macrogol-8-glycerides, substantially 5 % (w/w) to substantially 30 % (w/w) of polyoxy-35 castor oil, substantially 4.5 % (w/w) to substantially 20 % (w/w) of soy bean lecithin substantially 10 % (w/w) to substantially 35 % (w/w) of tocotrienols and substantially 2 % (w/w) to substantially 10 % (w/w) of tocopherol.

15 The composition in the aforementioned embodiment can be obtained by the mixing palm olein, caprylocaproyl macrogol-8-glycerides, and polyoxy-35 castor oil to obtain a homogeneous first mixture. Soy bean lecithin is further added into the first mixture and further mixing to obtain a homogeneous second mixture. Thereinafter, the
20 tocotrienols and tocopherols is then added into the second mixture and further mixing thereof until homogeneous.

Another embodiment of the present invention provides a composition comprises substantially 0.1 % (w/w) to substantially 10 % (w/w) of beeswax, substantially 0.5 %
25 (w/w) to substantially 50 % (w/w) of palm olein, substantially 1 % (w/w) to substantially 20 % (w/w) of caprylocaproyl macrogol-8-glycerides, substantially 5 % (w/w) to substantially 30 % (w/w) of polyoxy-35 castor oil, substantially 4.5 % (w/w) to substantially 20 % (w/w) of soy bean lecithin, substantially 10 % (w/w) to substantially 35 % (w/w) of tocotrienols, substantially 2 % (w/w) to substantially 10

% (w/w) of tocopherol, substantially 1.5 % (w/w) to substantially 7.5 % (w/w) of nicotinamide, substantially 0.01 % (w/w) to substantially 0.05% (w/w) of cyanocobalamine and substantially 0.02 % (w/w) to substantially 0.1 % (w/w) of folic acid.

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The composition in the aforementioned embodiment can be obtained by melting beeswax at 70 °C in a portion of palm olein. Separately, another portion of palm olein is mixed with caprylocaproyl macrogol-8-glycerides and polyoxy-35 castor oil to obtain a homogeneous first mixture. The first mixture is then homogeneously
10 combined with the beeswax in palm olein. Soy bean lecithin is further added into the first mixture and further mixing to obtain a homogeneous second mixture. In this embodiment, water-soluble vitamin powders of nicotinamide, cyanocobalamine and folic acid are sieved through 60 mesh and then added into the second mixture, followed by shearing and milling thereof. Thereinafter, the mixture of tocotrienols and
15 tocopherols is further added there into the second mixture, followed by mixing thereof until homogeneous.

Accordingly, the composition derived from the abovementioned method can be encapsulated into both soft and hard capsules. The recommended oral dosage for the
20 composition in the present invention is 2 capsules daily. Nonetheless, it shall be understood the dosage may vary for each individual.

The composition and method in producing the composition achieves an increase in extend of nutrient absorption in the intestine. Additionally, the novel composition
25 shows efficacy in replacing damaged sections of liver membrane hence improving hepatic regeneration thereof.

The present invention may be embodied in other specific forms without departing from its essential characteristics. The described embodiments are to be considered in

all aspects only as illustrative and not restrictive. The scope of the invention is, therefore indicated by the appended claims rather than by the foregoing description. All changes, which come within the meaning and range of equivalency of the claims, are to be embraced within their scope.