Claims

[Claim 1] A pharmaceutical composition for the prevention or treatment of non-alcoholic fatty liver disease comprising an insulinotropic peptide drug conjugate prepared by covalently linking an insulinotropic peptide and an immunoglobulin Fc region via a non-peptidyl polymer as an active ingredient, wherein the insulinotropic peptide is selected from the group consisting of exendin-4, an exendin-4 derivative prepared by deleting the N-terminal amine group of exendin-4, an exendin-4 derivative prepared by substituting the N-terminal amine group of exendin-4 with a hydroxyl group, an exendin-4 derivative prepared by modifying the N-terminal amine group of exendin-4 with a dimethyl group, and an exendin-4 derivative prepared by deleting alpha-carbon of the N-terminal histidine residue of exendin-4 and the N-terminal amine group linked to the alpha-carbon, and the non-peptidyl polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, copolymers of ethylene glycol-propylene glycol, polyoxyethylated polyols, polyvinyl alcohol, polysaccharides, dextran, polyvinyl ethyl ether, biodegradable polymers, lipid polymers, chitins, hyaluronic acid, and combinations thereof.

[Claim 2] The pharmaceutical composition according to claim 1, wherein the non-peptidyl polymer is linked to the amino acid residue other than the N-terminus of the insulinotropic peptide.

[Claim 3] The pharmaceutical composition according to claim 1, wherein the immunoglobulin Fc region and an amine group or a thiol group of the insulinotropic peptide are linked at both ends of the non-peptidyl polymer, respectively.

[Claim 4] The pharmaceutical composition according to claim 1, wherein the non-peptidyl polymer is linked to the lysine residue of the insulinotropic peptide.

[Claim 5] The pharmaceutical composition according to claim 1, wherein the non-peptidyl polymer is polyethylene glycol.

[Claim 6] The pharmaceutical composition according to claim 1, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 7] The pharmaceutical composition according to claim 1, wherein the immunoglobulin Fc region is composed of one to four domains selected from the group consisting of CH1, CH2, CH3 and CH4 domains.

[Claim 8] The pharmaceutical composition according to claim 7, wherein the im-

munoglobulin Fc region further include a hinge region.

[Claim 9] The pharmaceutical composition according to claim 1, wherein the immunoglobulin Fc region is an Fc region that is derived from an immunoglobulin selected from the group consisting of IgG, IgA, IgD, IgE and IgM.

[Claim 10] The pharmaceutical composition according to claim 9, wherein the immunoglobulin Fc region is an IgG4 Fc region.

[Claim 11] The pharmaceutical composition according to claim 10, wherein the immunoglobulin Fc region is a human non-glycosylated IgG4 Fc region.

[Claim 12] The pharmaceutical composition according to claim 1, wherein the reactive group of the non-peptidyl polymer is selected from the group consisting of an aldehyde group, a propionaldehyde group, a butyraldehyde group, a maleimide group and a succinimide derivative.

[Claim 13] The pharmaceutical composition according to claim 12, wherein the succinimide derivative is selected from the group consisting of succinimidyl propionate, succinimidyl carboxymethyl, hydroxy succinimidyl, and succinimidyl carbonate.

[Claim 14] The pharmaceutical composition according to claim 1, wherein the non-peptidyl polymer has reactive aldehyde groups at both ends thereof.

[Claim 15] The pharmaceutical composition according to claim 1, wherein the insulinotropic peptide drug conjugate increases the activity of PKC-ζ (Protein Kinase C-ζ) regulating the enzymatic activity involved in lipolysis.

[Claim 16] The pharmaceutical composition according to claim 1, wherein the insulinotropic peptide drug conjugate increases expression of Glut2 (Glucose transporter protein-2) involved in lipolysis.

[Claim 17] The pharmaceutical composition according to claim 1, wherein the non-alcoholic fatty liver disease is selected from the group consisting of simple steatosis, fatty liver diseases caused by malnutrition, starvation, obesity and diabetes, steatohepatitis, liver fibrosis and liver cirrhosis.

[Claim 18] A method for preventing or treating non-alcoholic liver disease, comprising the step of administering to a subject the pharmaceutical composition of any one of claims 1 to 17.

[CLAIMS]

1. A pharmaceutical composition for the prevention or treatment of non-alcoholic fatty liver disease comprising an insulinotropic peptide drug conjugate as an active ingredient, in which an insulinotropic peptide is covalently linked to an immunoglobulin Fc region via a non-peptidyl polymer,

wherein the insulinotropic peptide is selected from the group consisting of exendin-4, an exendin-4 derivative prepared by deleting the N-terminal amine group of exendin-4, an exendin-4 derivative prepared by substituting the N-terminal amine group of exendin-4 with a hydroxyl group, an exendin-4 derivative prepared by modifying the N-terminal amine group of exendin-4 with a dimethyl group, and an exendin-4 derivative prepared by deleting alpha-carbon of the N-terminal histidine residue of exendin-4 and the N-terminal amine group linked to the alpha-carbon, and

the non-peptidyl polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, copolymers of ethylene glycol-propylene glycol, polyoxyethylated polyols, polyvinyl alcohol, polysaccharides, dextran, polyvinyl ethyl ether, biodegradable polymers, lipid polymers, chitins, hyaluronic acid, and combinations thereof; and

wherein the non-peptidyl polymer is linked to Lysine residue at position 27 of the insulinotropic peptide.

3. The pharmaceutical composition according to claim

1, wherein the immunoglobulin Fc region and an amine group or a thiol group of the insulinotropic peptide are linked at both ends of the non-peptidyl polymer, respectively.

5. The pharmaceutical composition according to claim 1, wherein the non-peptidyl polymer is polyethylene glycol.

6. The pharmaceutical composition according to claim 1, wherein the immunoglobulin Fc region is aglycosylated.

7. The pharmaceutical composition according to claim 1, wherein the immunoglobulin Fc region is composed of one to four domains selected from the group consisting of CH1, CH2, CH3 and CH4 domains.

8. The pharmaceutical composition according to claim 7, wherein the immunoglobulin Fc region further include a hinge region.

9. The pharmaceutical composition according to claim 1, wherein the immunoglobulin Fc region is an Fc region that is derived from an immunoglobulin selected from the group consisting of IgG, IgA, IgD, IgE and IgM.

10. The pharmaceutical composition according to claim 9, wherein the immunoglobulin Fc region is an IgG4 Fc region.

11. The pharmaceutical composition according to claim

10, wherein the immunoglobulin Fc region is a human non-glycosylated IgG4 Fc region.

12. The pharmaceutical composition according to claim 1, wherein the reactive group of the non-peptidyl polymer is selected from the group consisting of an aldehyde group, a propionaldehyde group, a butyraldehyde group, a maleimide group and a succinimide derivative.

13. The pharmaceutical composition according to claim 12, wherein the succinimide derivative is selected from the group consisting of succinimidyl propionate, succinimidyl carboxymethyl, hydroxy succinimidyl, and succinimidyl carbonate.

14. The pharmaceutical composition according to claim 1, wherein the non-peptidyl polymer has reactive aldehyde groups at both ends thereof.

15. The pharmaceutical composition according to claim 1, wherein the insulinotropic peptide drug conjugate increases the activity of PKC-ζ (Protein Kinase C-ζ) regulating the enzymatic activity involved in lipolysis.

16. The pharmaceutical composition according to claim 1, wherein the insulinotropic peptide drug conjugate increases expression of Glut2 (Glucose transporter protein-2) involved in lipolysis.

17. The pharmaceutical composition according to claim 1, wherein the non-alcoholic fatty liver disease is selected from the group consisting of simple steatosis, fatty liver diseases caused by malnutrition, starvation, obesity and diabetes, steatohepatitis, liver fibrosis and liver cirrhosis.