

[CLAIMS]

[Claim 1]

A pharmaceutical composition for preventing or treating hyperlipidemia comprising an isolated peptide with activity to a glucagon receptor, a glucagon-like peptide-1 (GLP-1) receptor, and a glucose-dependent insulintropic polypeptide (GIP) receptor,

wherein the peptide comprises an amino acid sequence represented by General Formula 1 below:

Xaa1–Xaa2–Xaa3–Gly–Thr–Phe–Xaa7–Ser–Asp–Xaa10–Ser–Xaa12–
Xaa13–Xaa14–Xaa15–Xaa16–Xaa17–Xaa18–Xaa19–Xaa20–Xaa21–Phe–Xaa23–
Xaa24–Trp–Leu–Xaa27–Xaa28–Xaa29–Xaa30–R1 (General Formula 1, SEQ ID NO: 103)

wherein in General Formula 1 above, Xaa1 is histidine (His, H), 4-imidazoacetyl (CA), or tyrosine (Tyr, Y), Xaa2 is glycine (Gly, G), α -methyl-glutamic acid, or aminoisobutyric acid (Aib), Xaa3 is glutamic acid (Glu, E) or glutamine (Gln, Q), Xaa7 is threonine (Thr, T) or isoleucine (Ile, I), Xaa10 is leucine (Leu, L), tyrosine (Tyr, Y), lysine (Lys, K), cysteine (Cys, C), or valine (Val, V), Xaa12 is lysine (Lys, K), serine (Ser, S), or isoleucine (Ile, I), Xaa13 is glutamine (Gln, Q), tyrosine (Tyr, Y), alanine (Ala, A), or cysteine (Cys, C), Xaa14 is leucine (Leu, L), methionine (Met, M), or tyrosine (Tyr, Y), Xaa15 is cysteine (Cys, C), aspartic acid (Asp, D), glutamic acid (Glu, E), or leucine (Leu, L), Xaa16 is glycine (Gly, G), glutamic acid (Glu, E), or serine (Ser, S), Xaa17 is glutamine (Gln, Q), arginine (Arg, R), isoleucine (Ile, I), glutamic acid (Glu, E), cysteine (Cys, C), or lysine (Lys, K), Xaa18 is alanine (Ala, A), glutamine (Gln, Q), arginine (Arg, R), or histidine (His, H), Xaa19 is alanine (Ala, A), glutamine (Gln, Q), cysteine (Cys, C), or valine (Val, V), Xaa20 is lysine (Lys, K), glutamine (Gln, Q), or arginine (Arg, R), Xaa21 is glutamic acid (Glu, E), glutamine (Gln, Q), leucine (Leu, L), cysteine (Cys, C), or aspartic acid (Asp, D), Xaa23 is isoleucine (Ile, I) or valine (Val, V), Xaa24 is alanine (Ala, A), glutamine (Gln, Q), cysteine (Cys, C), asparagine (Asn, N), aspartic acid (Asp, D), or glutamic acid (Glu, E), Xaa27 is valine (Val, V), leucine (Leu, L), or lysine (Lys, K), ~~or methionine (Met, M)~~, Xaa28 is cysteine (Cys, C), lysine (Lys, K), alanine (Ala, A), asparagine (Asn, N), or aspartic acid (Asp, D), Xaa29 is cysteine (Cys, C), glycine (Gly, G), glutamine (Gln, Q), threonine (Thr, T), glutamic

acid (Glu, E), or histidine (His, H), Xaa30 is cysteine (Cys, C), glycine (Gly, G), lysine (Lys, K), or histidine (His, H), or is absent, and

R1 is cysteine (Cys, C), GKKNDWKHNIT (SEQ ID NO: 106), m-SSGAPPPS-n (SEQ ID NO: 107), or m-SSGQPPPS-n (SEQ ID NO: 108), or is absent,

wherein m is -Cys-, -Pro-, or -Gly-Pro-, and n is -Cys-, -Gly-, -Ser-, or -His-Gly-, or is absent.

[Claim 2]

The pharmaceutical composition of claim 1, wherein in General Formula 1 above, Xaa14 is leucine or methionine, and Xaa15 is cysteine, aspartic acid, or leucine.

[Claim 3]

The pharmaceutical composition of claim 1, wherein in General Formula 1 above, Xaa2 is glycine, α -methyl-glutamic acid, or Aib, Xaa7 is threonine, Xaa10 is tyrosine, cysteine, or valine, Xaa12 is lysine or isoleucine, Xaa13 is tyrosine, alanine, glutamine, or cysteine, Xaa14 is leucine, cysteine, or methionine, Xaa15 is cysteine, leucine, glutamic acid, or aspartic acid, Xaa17 is glutamine, arginine, isoleucine, cysteine, glutamic acid, or lysine, Xaa18 is alanine, glutamine, arginine, or histidine, Xaa19 is alanine, glutamine, valine, or cysteine, Xaa20 is lysine, arginine, or glutamine, Xaa21 is glutamic acid, glutamine, leucine, cysteine, or aspartic acid, Xaa23 is isoleucine or valine, Xaa24 is cysteine, alanine, glutamine, asparagine, glutamic acid, or aspartic acid, and Xaa27 is leucine or lysine.

[Claim 4]

The pharmaceutical composition of claim 1, wherein the peptide is a peptide comprising an amino acid sequence of General Formula 2 below:

Xaa1-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Xaa10-Ser-Lys-Xaa13-Xaa14-Xaa15-Xaa16-Xaa17-Xaa18-Xaa19-Xaa20-Xaa21-Phe-Xaa23-Xaa24-Trp-Leu-Leu-Xaa28-Xaa29-Xaa30-Xaa31-Ser-Ser-Gly-Gln-Pro-Pro-Pro-Ser-Xaa40 (General Formula 2, SEQ ID NO: 104)

wherein in General Formula 2 above, Xaa1 is 4-imidazoacetyl, histidine, or tyrosine, Xaa2 is glycine, α -methyl-glutamic acid, or Aib, Xaa10 is tyrosine, or cysteine, Xaa13 is alanine, glutamine, tyrosine, or cysteine, Xaa14 is leucine, methionine, or

tyrosine, Xaa15 is aspartic acid, glutamic acid, or leucine, Xaa16 is glycine, glutamic acid, or serine, Xaa17 is glutamine, arginine, isoleucine, glutamic acid, cysteine, or lysine, Xaa18 is alanine, glutamine, arginine, or histidine, Xaa19 is alanine, glutamine, cysteine, or valine, Xaa20 is lysine, glutamine, or arginine, Xaa21 is cysteine, glutamic acid, glutamine, leucine, or aspartic acid, Xaa23 is isoleucine or valine, Xaa24 is cysteine, alanine, glutamine, asparagine, or glutamic acid, Xaa28 is lysine, cysteine, asparagine, or aspartic acid, Xaa29 is glycine, glutamine, cysteine, or histidine, Xaa30 is cysteine, glycine, lysine, or histidine, Xaa31 is proline or cysteine, and Xaa40 is cysteine, or is absent.

[Claim 5]

The pharmaceutical composition of claim 1, wherein in General Formula 1 above, Xaa2 is glycine, α -methyl-glutamic acid, or Aib, Xaa7 is threonine, Xaa10 is tyrosine, cysteine, or valine, Xaa12 is lysine or isoleucine, Xaa13 is tyrosine, alanine, or cysteine, Xaa14 is leucine or methionine, Xaa15 is cysteine or aspartic acid, Xaa17 is glutamine, arginine, isoleucine, cysteine, or lysine, Xaa18 is alanine, arginine, or histidine, Xaa19 is alanine, glutamine, or cysteine, Xaa20 is lysine or glutamine, Xaa21 is glutamic acid, cysteine, or aspartic acid, Xaa23 is valine, Xaa24 is alanine, glutamine, cysteine, asparagine, or aspartic acid, and Xaa27 is leucine or lysine.

[Claim 6]

The pharmaceutical composition of claim 2, wherein in General Formula 2 above, Xaa13 is alanine, tyrosine, or cysteine, Xaa15 is aspartic acid or glutamic acid, Xaa17 is glutamine, arginine, cysteine, or lysine, Xaa18 is alanine, arginine, or histidine, Xaa21 is cysteine, glutamic acid, glutamine, or aspartic acid, Xaa23 is isoleucine or valine, Xaa24 is cysteine, glutamine, or asparagine, Xaa28 is cysteine, asparagine, or aspartic acid, Xaa29 is glutamine, cysteine, or histidine, and Xaa30 is cysteine, lysine, or histidine.

[Claim 7]

The pharmaceutical composition of claim 1, wherein in General Formula 1 above, Xaa2 is α -methyl-glutamic acid or Aib, Xaa7 is threonine, Xaa10 is tyrosine or cysteine, Xaa12 is lysine or isoleucine, Xaa13 is tyrosine, alanine, or cysteine, Xaa14

is leucine or methionine, Xaa15 is cysteine or aspartic acid, Xaa16 is glutamic acid, Xaa17 is arginine, isoleucine, cysteine, or lysine, Xaa18 is alanine, arginine, or histidine, Xaa19 is alanine, glutamine, or cysteine, Xaa20 is lysine or glutamine, Xaa21 is glutamic acid or aspartic acid, Xaa23 is valine, Xaa24 is glutamine, asparagine, or aspartic acid, Xaa27 is leucine, and Xaa28 is cysteine, alanine, asparagine, or aspartic acid.

[Claim 8]

The pharmaceutical composition of claim 1, wherein in General Formula 1 above, Xaa1 is histidine or 4-imidazoacetyl, Xaa2 is α -methyl-glutamic acid or Aib, Xaa3 is glutamine, Xaa7 is threonine, Xaa10 is tyrosine, Xaa12 is isoleucine, Xaa13 is alanine or cysteine, Xaa14 is methionine, Xaa15 is aspartic acid, Xaa16 is glutamic acid, Xaa17 is isoleucine or lysine, Xaa18 is alanine or histidine, Xaa19 is glutamine or cysteine, Xaa20 is lysine, Xaa21 is aspartic acid, Xaa23 is valine, Xaa24 is asparagine, Xaa27 is leucine, Xaa28 is alanine or asparagine, Xaa29 is glutamine or threonine, and Xaa30 is cysteine or lysine, or is absent.

[Claim 9]

The pharmaceutical composition of claim 1, wherein the peptide is a peptide comprising an amino acid sequence of General Formula 3 below:

Xaa1–Xaa2–Gln–Gly–Thr–Phe–Thr–Ser–Asp–Tyr–Ser–Lys–Xaa13–Leu–
Asp–Glu–Xaa17–Xaa18–Xaa19–Lys–Xaa21–Phe–Val–Xaa24–Trp–Leu–Leu–
Xaa28–Xaa29–Xaa30–Xaa31–Ser–Ser–Gly–Gln–Pro–Pro–Pro–Ser–Xaa40
(General Formula 3, SEQ ID NO: 105),

wherein in General Formula 3 above, Xaa1 is histidine or tyrosine, Xaa2 is α -methyl-glutamic acid or Aib, Xaa13 is alanine, tyrosine or cysteine, Xaa17 is arginine, cysteine, or lysine, Xaa18 is alanine or arginine, Xaa19 is alanine or cysteine, Xaa21 is glutamic acid or aspartic acid, Xaa24 is glutamine or asparagine, Xaa28 is cysteine or aspartic acid, Xaa29 is cysteine, histidine, or glutamine, Xaa30 is cysteine or histidine, Xaa31 is proline or cysteine, and Xaa40 is cysteine, or is absent.

[Claim 10]

The pharmaceutical composition of claim 1, wherein R1 is cysteine,

GKKNDWKHNIT (SEQ ID NO: 106), CSSGQPPPS (SEQ ID NO: 109), GPSSGAPPPS (SEQ ID NO: 110), GPSSGAPPPSC (SEQ ID NO: 111), PSSGAPPPS (SEQ ID NO: 112), PSSGAPPPSG (SEQ ID NO: 113), PSSGAPPPSHG (SEQ ID NO: 114), PSSGAPPPSS (SEQ ID NO: 115), PSSGQPPPS (SEQ ID NO: 116), or PSSGQPPPS (SEQ ID NO: 117), or is absent.

[Claim 11]

The pharmaceutical composition of claim 1, wherein the peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 11, and 13 to 102.

[Claim 12]

The pharmaceutical composition of any one of claims 1 to 9, wherein a ring is formed between a 16th amino acid and a 20th amino acid from the N-terminus of the general formulae.

[Claim 13]

The pharmaceutical composition of any one of claims 1 to 11, wherein the C-terminus of the peptide is amidated.

[Claim 14]

The pharmaceutical composition of any one of claims 1 to 11, wherein the pharmaceutical composition has at least one of the effects on increasing LDL absorption, inhibiting the activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), and promoting fatty acid degradation.

[Claim 15]

A pharmaceutical composition for preventing or treating hyperlipidemia comprising a conjugate represented by Chemical Formula 1 below,

[Chemical Formula 1]

X-L_a-F

wherein X is a peptide with activity to a glucagon receptor, a GLP-1 receptor,

and a GIP receptor,

L is polyethylene glycol,

a is 0 or a natural number, where when a is 2 or greater, each L is independent,

F is an immunoglobulin Fc region; and

the peptide is a peptide comprising an amino acid sequence represented by General Formula 1 below:

Xaa1–Xaa2–Xaa3–Gly–Thr–Phe–Xaa7–Ser–Asp–Xaa10–Ser–Xaa12–
Xaa13–Xaa14–Xaa15–Xaa16–Xaa17–Xaa18–Xaa19–Xaa20–Xaa21–Phe–Xaa23–
Xaa24–Trp–Leu–Xaa27–Xaa28–Xaa29–Xaa30–R1 (General Formula 1, SEQ ID
NO: 103)

wherein in General Formula 1 above,

Xaa1 is histidine (His, H), 4-imidazoacetyl (CA), or tyrosine (Tyr, Y),

Xaa2 is glycine (Gly, G), α-methyl-glutamic acid, or aminoisobutyric acid (Aib),

Xaa3 is glutamic acid (Glu, E) or glutamine (Gln, Q),

Xaa7 is threonine (Thr, T) or isoleucine (Ile, I),

Xaa10 is leucine (Leu, L), tyrosine (Tyr, Y), lysine (Lys, K), cysteine (Cys, C),
or valine (Val, V),

Xaa12 is lysine (Lys, K), serine (Ser, S), or isoleucine (Ile, I),

Xaa13 is glutamine (Gln, Q), tyrosine (Tyr, Y), alanine (Ala, A), or cysteine (Cys,
C),

Xaa14 is leucine (Leu, L), methionine (Met, M), or tyrosine (Tyr, Y),

Xaa15 is cysteine (Cys, C), aspartic acid (Asp, D), glutamic acid (Glu, E), or
leucine (Leu, L),

Xaa16 is glycine (Gly, G), glutamic acid (Glu, E), or serine (Ser, S),

Xaa17 is glutamine (Gln, Q), arginine (Arg, R), isoleucine (Ile, I), glutamic acid
(Glu, E), cysteine (Cys, C), or lysine (Lys, K),

Xaa18 is alanine (Ala, A), glutamine (Gln, Q), arginine (Arg, R), or histidine (His,
H),

Xaa19 is alanine (Ala, A), glutamine (Gln, Q), cysteine (Cys, C), or valine (Val,
V),

Xaa20 is lysine (Lys, K), glutamine (Gln, Q), or arginine (Arg, R),

Xaa21 is glutamic acid (Glu, E), glutamine (Gln, Q), leucine (Leu, L), cysteine
(Cys, C), or aspartic acid (Asp, D),

Xaa23 is isoleucine (Ile, I) or valine (Val, V),

Xaa24 is alanine (Ala, A), glutamine (Gln, Q), cysteine (Cys, C), asparagine (Asn, N), aspartic acid (Asp, D), or glutamic acid (Glu, E),

Xaa27 is valine (Val, V), leucine (Leu, L), or lysine (Lys, K), ~~or methionine (Met, M),~~

Xaa28 is cysteine (Cys, C), lysine (Lys, K), alanine (Ala, A), asparagine (Asn, N), or aspartic acid (Asp, D),

Xaa29 is cysteine (Cys, C), glycine (Gly, G), glutamine (Gln, Q), threonine (Thr, T), glutamic acid (Glu, E), or histidine (His, H),

Xaa30 is cysteine (Cys, C), glycine (Gly, G), lysine (Lys, K), or histidine (His, H), or is absent, and

R1 is cysteine (Cys, C), GKKNDWKHNIT (SEQ ID NO: 106), m-SSGAPPPS-n (SEQ ID NO: 107), or m-SSGQPPPS-n (SEQ ID NO: 108), or is absent,

wherein m is -Cys-, -Pro-, or -Gly-Pro-, and

n is -Cys-, -Gly-, -Ser-, or -His-Gly-, or is absent.

[Claim 16]

The pharmaceutical composition of claim 15, wherein the immunoglobulin Fc region is an IgG Fc region.

[Claim 17]

The pharmaceutical composition of claim 15, wherein the pharmaceutical composition has at least one of the effects on increasing LDL absorption, inhibiting the activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), and promoting fatty acid degradation.

[Claim 18]

The pharmaceutical composition of claim 1, wherein after 24 to 48 hours from administration of the pharmaceutical composition, the activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is less than 50%.

[Claim 19]

The pharmaceutical composition of claim 1, wherein the pharmaceutical

composition reduces the triglyceride level and the LDL level in blood.