Still another object of the present invention is to provide a composition containing the conjugate.

Still another object of the present invention is to provide a method for treating a target disease, which includes administering the conjugate or a composition containing the conjugate to a subject in need thereof.

Still another object of the present invention is to provide a use of the conjugate or composition thereof for use in the preparation of a medicament.

[Technical Solution]

To achieve the above objects, in an example, the present disclosure provides a conjugate of a peptide having activities to a glucagon receptor, a glucagon-like peptide-1 (GLP-1) receptor, and a glucose-dependent insulinotropic polypeptide (GIP) receptor.

In one aspect, the present disclosure refers to a conjugate represented by Chemical Formula 1 below:

[Chemical Formula 1]

X - La - F

wherein,

X is a peptide having activities to a glucagon receptor, a glucagon-like peptide-1 (GLP-1) receptor, and a glucose-dependent insulinotropic polypeptide (GIP) receptor;

L is a linker;

a is 0 or a positive integer, with the proviso that when a is 2 or greater, each L is independent from each other; and

F is a material capable of increasing the half-life of X,wherein X 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,

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 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);
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.

In one example, the present disclosure refers to a conjugate represented by Chemical Formula 1 below:

[Chemical Formula 1]

X - La - F

wherein,

X is a peptide having activities to a glucagon receptor, a glucagon-like peptide-1 (GLP-1) receptor, and a glucose-dependent insulinotropic polypeptide (GIP) receptor;

L is a linker;

a is 0 or a positive integer, with the proviso that when a is 2 or greater, each L is independent from each other; and

F is a material capable of increasing the half-life of X.

In another aspect, the present disclosure refers to a conjugate represented by Chemical Formula 1 below:

[Chemical Formula 1]

X - La - F

wherein,

X is a peptide having activities to a glucagon receptor, a glucagon-like peptide-1 (GLP-1) receptor, and a glucose-dependent insulinotropic polypeptide (GIP) receptor;

L is a linker;

a is 0 or a positive integer, with the proviso that when a is 2 or greater, each L is independent from each other; and

F is a material capable of increasing the half-life of X,

wherein X is a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 102.

In another aspect, the present disclosure refers to the use of a peptide as described herein in the manufacture of a medicament for preventing or treating a metabolic syndrome. In another example, the present disclosure refers to a pharmaceutical composition for preventing or treating metabolic syndrome comprising a conjugate as disclosed herein.

In a specific example, X is an analog of native glucagon with a variation selected from the group consisting of substitution, addition, deletion, modification, and a combination thereof, on at least one amino acid of the native glucagon sequence.

In still another specific example, the amino acid sequence with addition is derived from a native GLP-1 amino acid sequence, a native GIP amino acid sequence, or a native exendin-4 amino acid sequence.

In still another specific example, the X is a peptide including 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,

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

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

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), 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);

Claims

1. A conjugate represented by Chemical Formula 1 below:

[Chemical Formula 1]
X - La - F

wherein,
X is a peptide having activities to a glucagon receptor, a glucagon-like peptide-1 (GLP-1) receptor, and a glucose-dependent insulinotropic polypeptide (GIP) receptor;
L is a linker;
a is 0 or a positive integer, with the proviso that when a is 2 or greater, each L is independent from each other; and
F is a material capable of increasing the half-life of X,wherein X 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,
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 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);
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.

2. The conjugate of claim 1,
wherein Xaa14 is leucine or methionine; and
Xaa15 is cysteine, aspartic acid, or leucine.

3. The conjugate of claim 1,
wherein, in General Formula 1,
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, tyrosine, 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 valine;
Xaa24 is cysteine, alanine, glutamine, asparagine, glutamic acid, or aspartic acid; and
Xaa27 is leucine or lysine.

4. The conjugate of claim 1, wherein X is a peptide comprising an amino acid sequence represented by 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,
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 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.

5. The conjugate of claim 1,
wherein, in General Formula 1,
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.

6. The conjugate of claim 4,
wherein, in General Formula 2,
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 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.

7. The conjugate of claim 1,
wherein, in General Formula 1,
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.

8. The conjugate of claim 1,

wherein, in General Formula 1,
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.

9. The conjugate of claim 1,
wherein X is a peptide comprising an amino acid sequence represented by 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,
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.

10. The conjugate 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 PSSGQPPPSC (SEQ ID NO: 117), or is absent.

11. The conjugate according to any one of claims 1 to 10, wherein, in General Formulas 1 to 3, the 16th amino acid and the 20th amino acid from the N-terminus together form a ring.

12. A conjugate represented by Chemical Formula 1 below:

[Chemical Formula 1]
X - La - F

wherein,
X is a peptide having activities to a glucagon receptor, a glucagon-like peptide-1 (GLP-1) receptor, and a glucose-dependent insulinotropic polypeptide (GIP) receptor;
L is a linker;
a is 0 or a positive integer, with the proviso that when a is 2 or greater, each L is independent from each other; and
F is a material capable of increasing the half-life of X,
wherein X is a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 102.

13. The conjugate according to any one of claims 1 to 10, wherein F is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an in vivo connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

14. The conjugate of claim 13, wherein the polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitins, hyaluronic acid, an oligonucleotide, and a combination thereof.

15. The conjugate according to any one of claims 1 to 10, wherein F is an immunoglobulin Fc region.

16. The conjugate of claim 15, wherein F is an IgG Fc region.

17. The conjugate according to any one of claims 1 to 10, wherein L is a peptide, fatty acid, a saccharide, a polymer, a low molecular weight compound, a nucleotide, or a combination thereof.

18. The conjugate of claim 17, wherein the polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitins, hyaluronic acid, an oligonucleotide, and a combination thereof.

19. The conjugate according to any one of claims 1 to 10, wherein L is polyethylene glycol.

20. Use of a peptide according to any one of claims 1 to 10 in the manufacture of a medicament for preventing or treating a metabolic syndrome.

21. The use of claim 20, wherein the metabolic syndrome comprises impaired glucose tolerance, hypercholesterolemia, dyslipidemia, obesity, diabetes, hypertension, arteriosclerosis due to dyslipidemia, atherosclerosis, arteriosclerosis, or coronary heart disease.