



US012667602B2

(12) **United States Patent**
Yun et al.

(10) **Patent No.:** **US 12,667,602 B2**
(45) **Date of Patent:** **Jun. 30, 2026**

(54) **COMPOSITION FOR PREVENTING, TREATING OR ALLEVIATING DIABETES, COMPRISING LGI3-DERIVED PEPTIDE AS AN ACTIVE INGREDIENT**

(71) Applicant: **CHUNG-ANG UNIVERSITY INDUSTRY-ACADEMIC COOPERATION FOUNDATION,**
Seoul (KR)

(72) Inventors: **Hye-Young Yun,** Seoul (KR);
Dong-Seok Kim, Seoul (KR)

(73) Assignee: **CHUNG-ANG UNIVERSITY INDUSTRY-ACADEMIC COOPERATION FOUNDATION,**
Seoul (KR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1016 days.

(21) Appl. No.: **17/625,437**

(22) PCT Filed: **Jul. 8, 2020**

(86) PCT No.: **PCT/KR2020/008879**

§ 371 (c)(1),

(2) Date: **Jan. 7, 2022**

(87) PCT Pub. No.: **WO2021/006607**

PCT Pub. Date: **Jan. 14, 2021**

(65) **Prior Publication Data**

US 2022/0257708 A1 Aug. 18, 2022

(30) **Foreign Application Priority Data**

Jul. 9, 2019 (KR) 10-2019-0082713

(51) **Int. Cl.**

A61K 38/17 (2006.01)

A61K 38/10 (2006.01)

A61P 1/16 (2006.01)

A61P 1/18 (2006.01)

A61P 3/00 (2006.01)

A61P 3/10 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 38/1709** (2013.01); **A61K 38/10** (2013.01); **A61P 1/16** (2018.01); **A61P 1/18** (2018.01); **A61P 3/00** (2018.01); **A61P 3/10** (2018.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2009/0221479 A1 9/2009 Barker
2016/0137748 A1 5/2016 Young
2022/0026443 A1* 1/2022 Oh G01N 33/6893

FOREIGN PATENT DOCUMENTS

KR 20190135378 A 12/2019
WO 2014202978 A1 12/2014
WO WO-2020101251 A1* 5/2020 G01N 33/6893

OTHER PUBLICATIONS

MedlinePlus, "Metabolic Disorders," available online at <https://medlineplus.gov/metabolicdisorders.html>, 6 pages (2016) (Year: 2016).*

UniProt Accession No. Q8N145, 13 pages (2002) (Year: 2002).*
Monostra, "Fatty pancreas increases diabetes risk, but may be reversible with weight loss", Healio.com, available online at <https://www.healio.com/news/endocrinology/20221202/fatty-pancreas-increases-diabetes-risk-but-may-be-reversible-with-weight-loss>, 5 pages (2022) (Year: 2022).*

Radlinger et al., Curr. Diabetes Rep. 20:18 (7 pages) (2020) (Year: 2020).*

Chen et al., Molec. Cellul. Proteomics 7:2323-2336 (2008) (Year: 2008).*

Yin et al., Metabol. Clin. Exp. 57:712-717 (2008) (Year: 2008).*

Tian et al., Biosci. Rep. 38:1-9 (2018) (Year: 2018).*

International Search Report for App. No. PCT/KR2020/008879, dated Oct. 22, 2020, 4 pages.

Kim et al., "Leucine-rich glioma inactivated 3 regulates adipogenesis through ADAM23", Biochimica et Biophysica Acta 1821, 2012, 914-922.

Liu et al., "Nonerythropoietic Erythropoietin-Derived Peptide Suppresses Adipogenesis, Inflammation, Obesity and Insulin Resistance", Scientific Reports, 5:15134, DOI: 10.1038/srep15134, 16 pages, published 2015.

* cited by examiner

Primary Examiner — Thea D'Ambrosio

(74) *Attorney, Agent, or Firm* — Riverside Law LLP

(57) **ABSTRACT**

The present invention relates to a composition and the like, for preventing, treating or alleviating diabetes, comprising an LGI3-derived peptide as an effective component. The composition comprising, as an active ingredient, an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 of the present invention exhibits an inhibitory effect on weight gain, elevation of blood glucose levels, pancreas and liver damage, elevation of blood lipid levels, and an increase of insulin resistance indexes accompanied by diabetes and diabetes-associated metabolic disorders associated with diabetes, and thus can prevent, treat, or alleviate diabetes and metabolic disorders associated with diabetes.

2 Claims, 12 Drawing Sheets

Specification includes a Sequence Listing.

FIG. 1

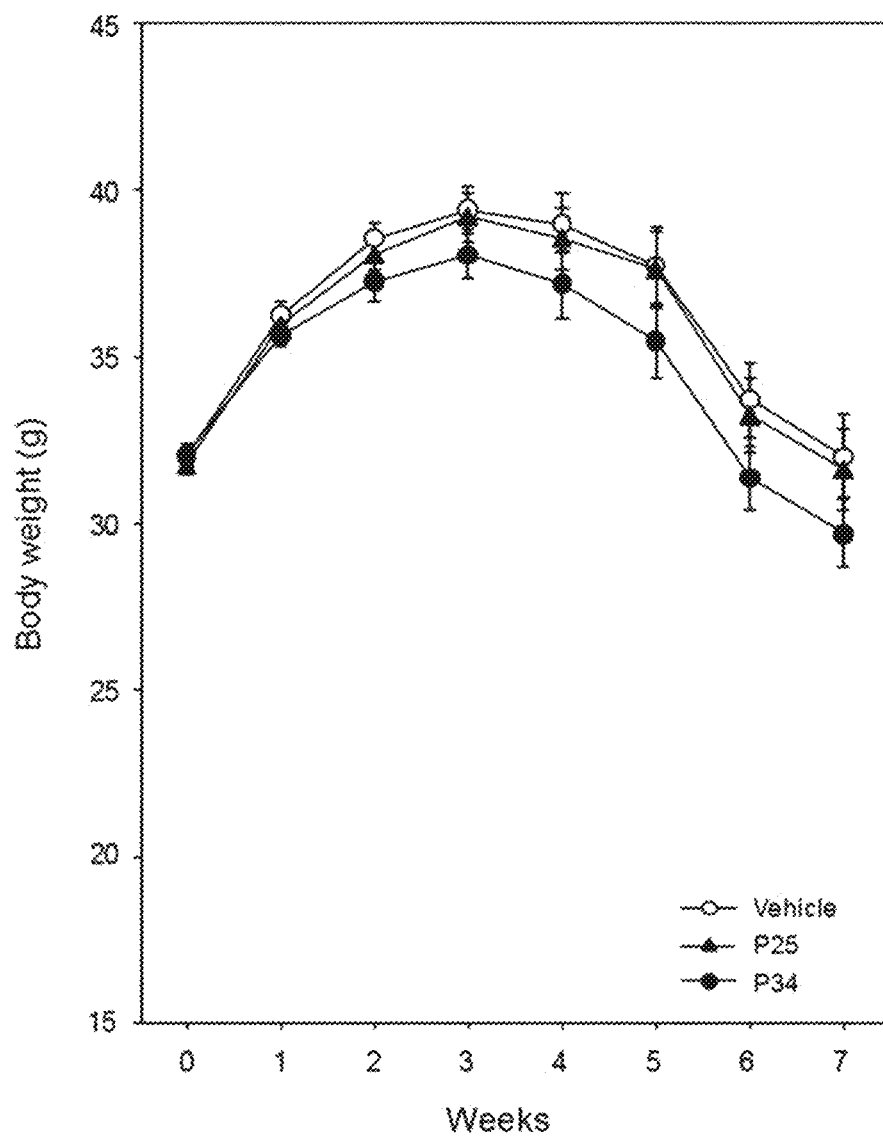


FIG. 2

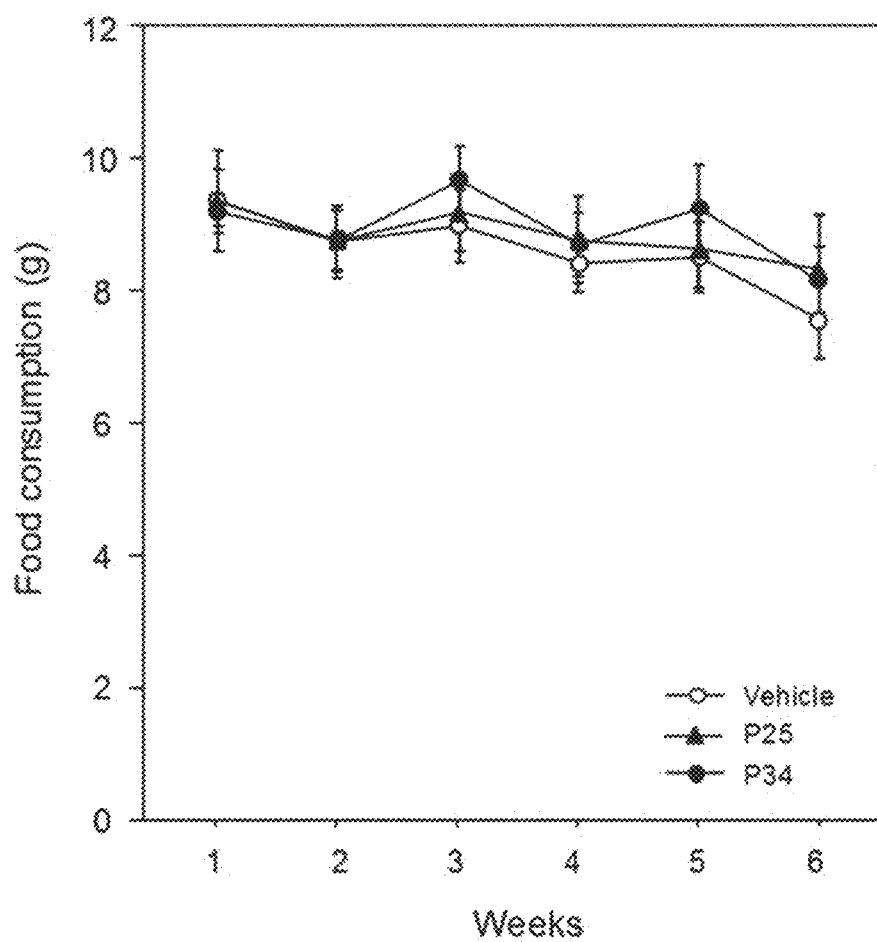


FIG. 3

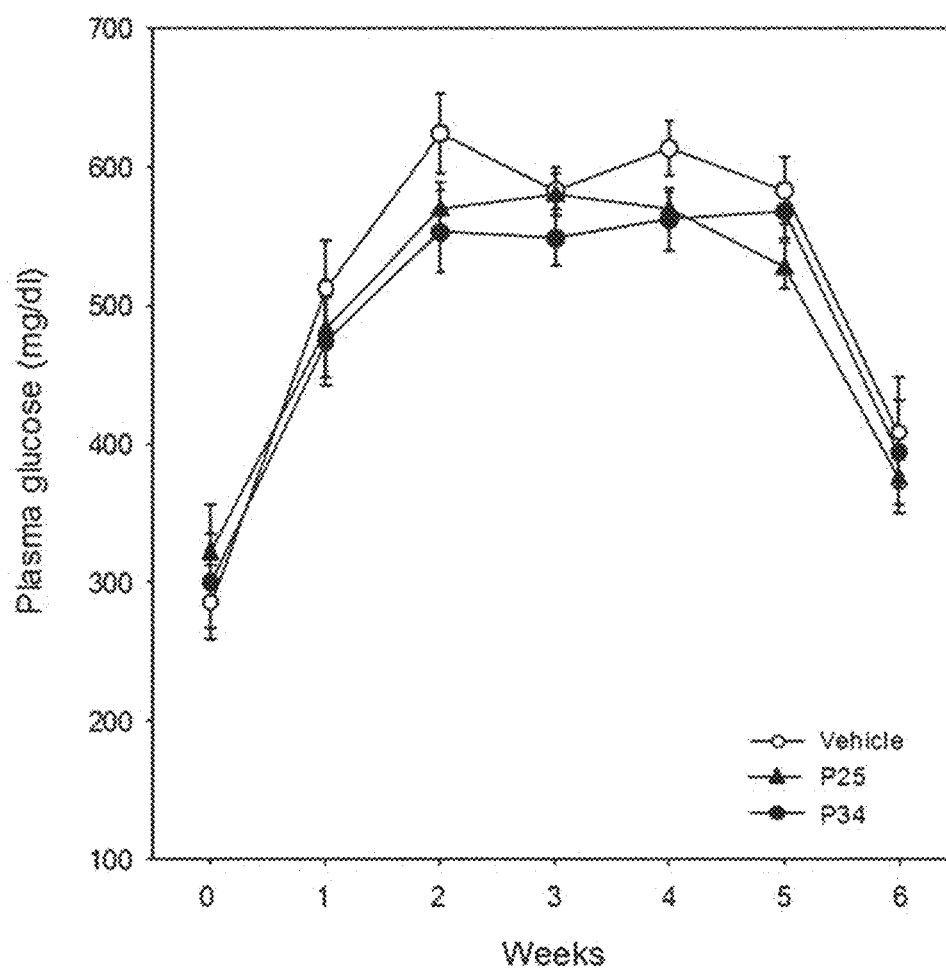


FIG. 4A

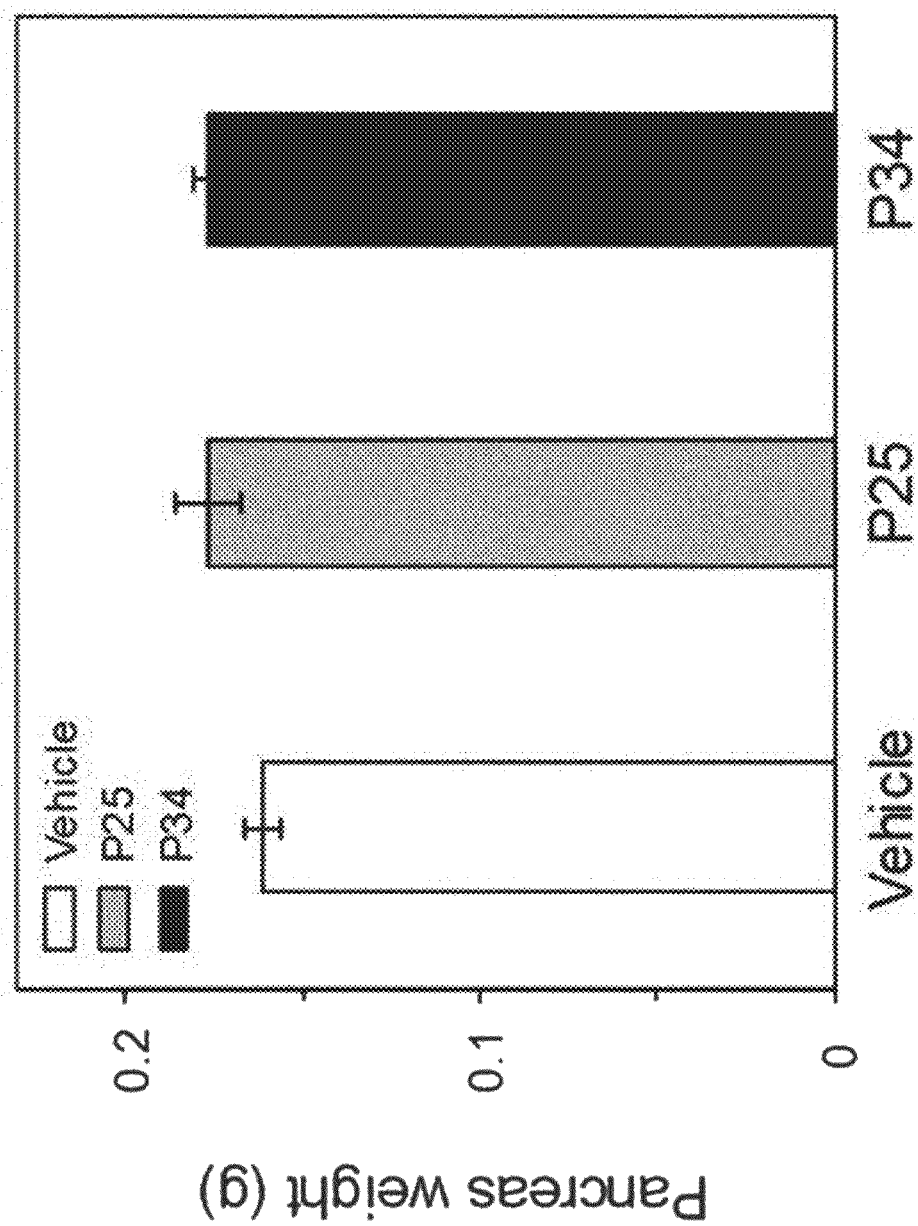


FIG. 4B

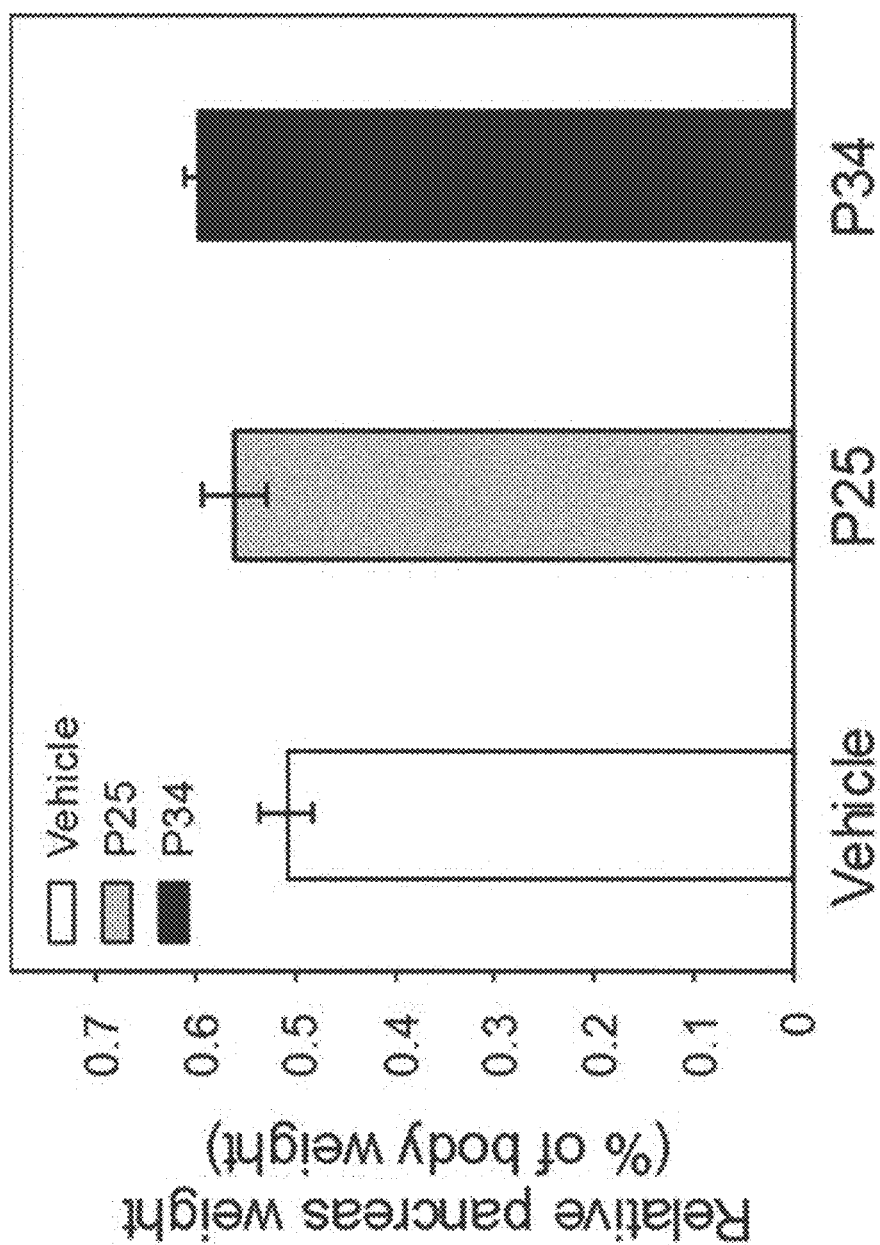


FIG. 5A

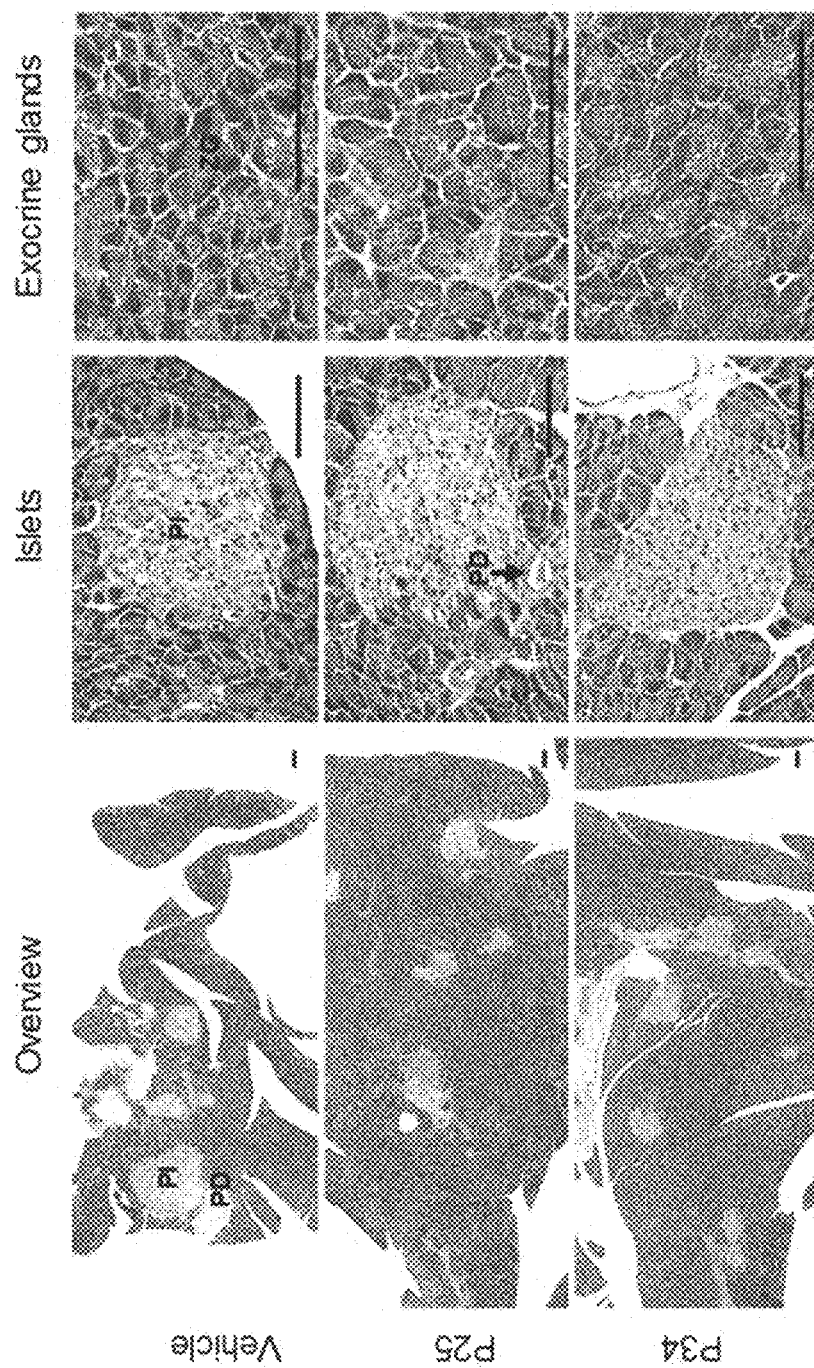


FIG. 5B

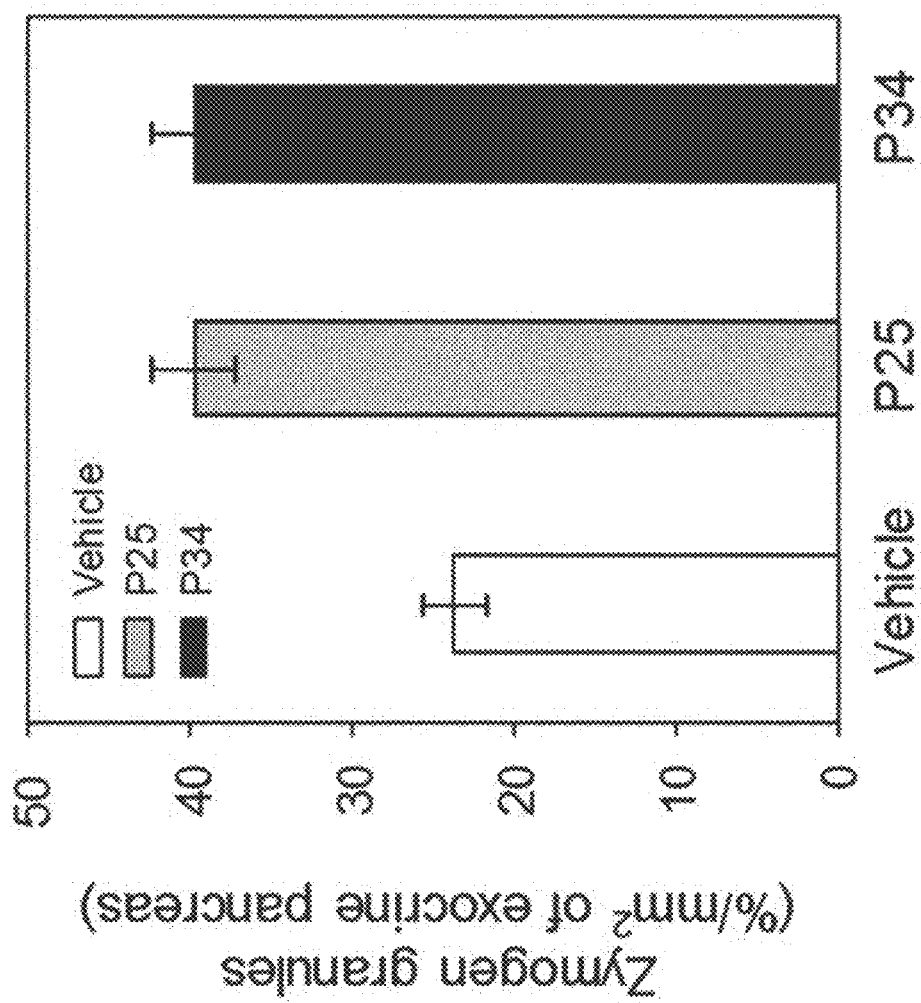


FIG. 6A

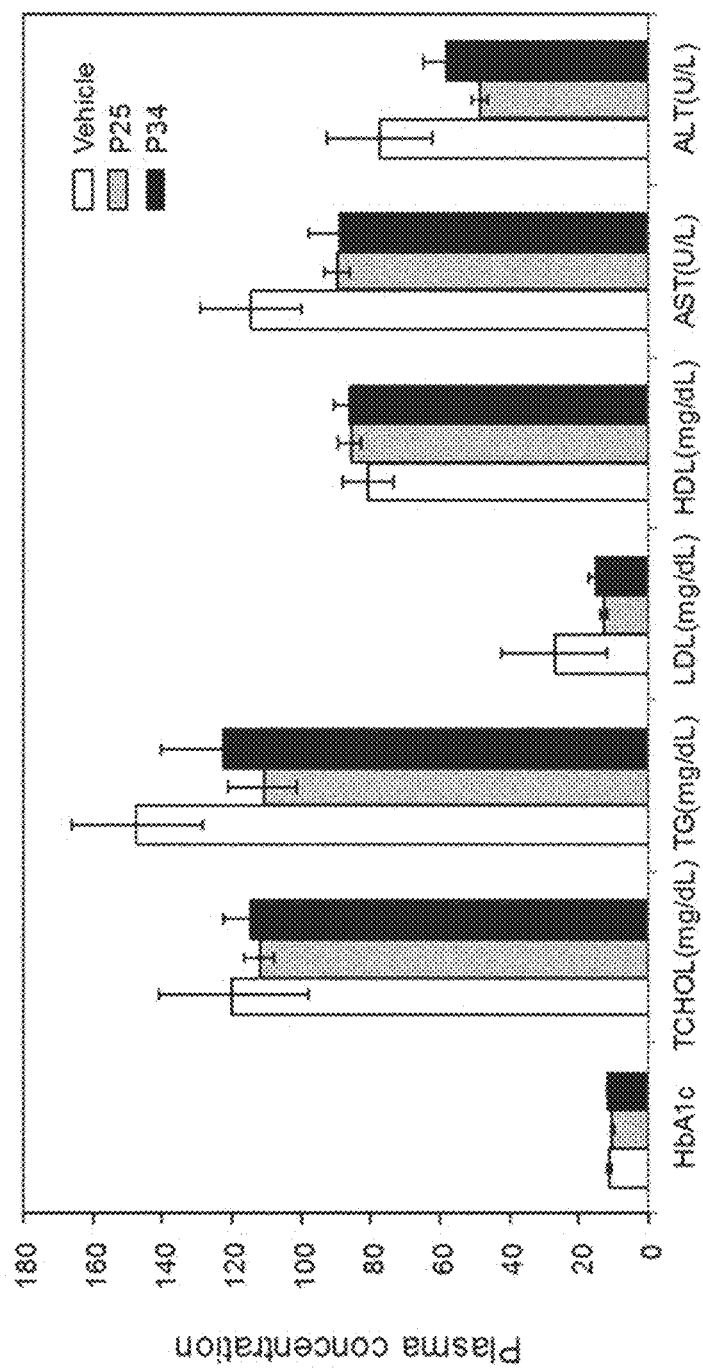


FIG. 6B

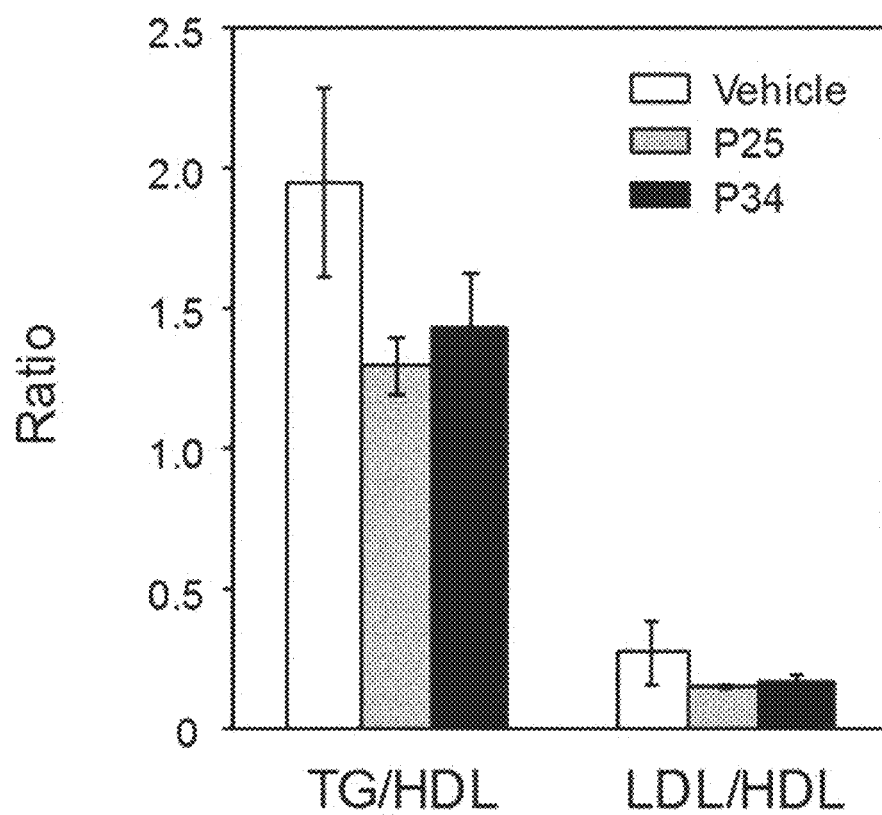


FIG. 7A

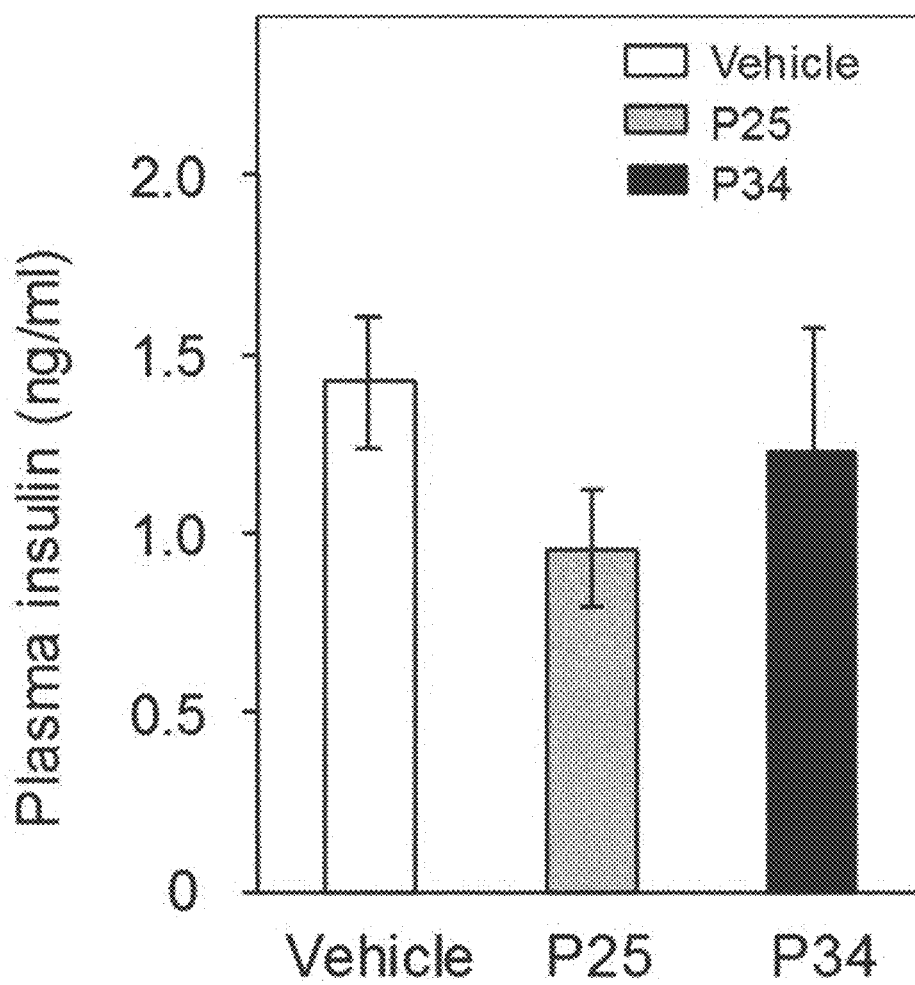


FIG. 7B

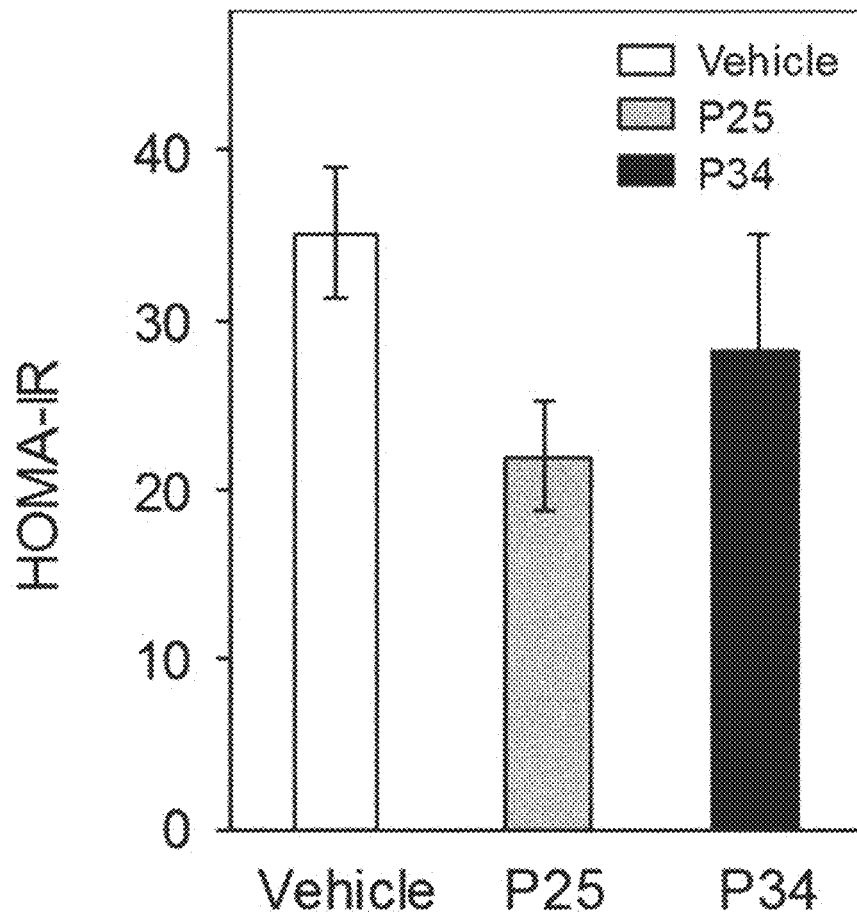


FIG. 8

Human	1	MAGLRKGGPGPCLLALSAIGRCIMIQVSAKRPPKTPCPFPSCSCTROTAFQVDSKAVR
Mouse	1	MAGLRKPGGGRLLVLTILGRCIMIQVSAKRPPKTPCPFPSCSCTROTAFQVDSKSVR
Human	61	NLPSEVISLTLVNAARFEIQDCAFSHUPLIQFLLNSNKFLLIGNAFTGLSHLQYLFIE
Mouse	61	NLPSEVISLTLVNAARFEIQDCAFSHUPLIQFLLNSNKFLLIGNAFTGLSHLQYLFIE
Human	121	NNDIWALSKEFTFRGLKSLTHLSLANNHQLTRPRDIFRPDLINDLDRGNSLNCDGVNR
Mouse	121	NNDIWALSKEFTFRGLKSLTHLSLANNHQLTRPRDIFRPDLILSDLDLRGNA LNCDGVNR
Human	181	LVEWLAHTNTTVARIYCASPPREFQSHRYQDLPILREFDCITTDVLYQTLAPPAVSAEPFL
Mouse	181	LVEWLAHTNTTVARIYCASPPREFQSHRYQDLPILREFDCITTDVLYQTLSPPAVSAEPFL
Human	241	YSSDLYLALAQFCVSACTILKWDYVERQLRDYRIPAPSAVHCXPNWVD5QLYVWVAQLF
Mouse	241	YSSDLYLALAQFCASACTILKWDYVERQLRDYRIPAPSAVHCXPNWVD5QLYVWVAQLF
Human	301	GGSYTYHWDDNTTFTNLIQDIDFQVRKPNDLKAFRIDGDMYFAVADSSKAGATSLYRHH
Mouse	301	GGSYTYHWDDNTTFTNLIQDIDFQVRKPNDLKAFRIDGDMYFAVADSSKAGATSLYRHH
Human	361	QNGFYSHCALHPWHRDIDLEFVDGKRPRLIVSSSSQAPVIYQMSRTOKQFVAQCEVTQV
Mouse	361	QNGFYSHQYTHANRRVTDLEFVDGKRPRLIVSSSSQAPVIYQMSR5KQQFVAQCEVTQV
		P25
Human	421	PDAQAVKHFACRQSYLCLSRVIGDSKILRWEGTRFSEYQALPSRGSLALQFFLVGGREY
Mouse	421	PDAQAVKHFACRQSYLCLSRVIGDSKILRWEGTRFSEYQALPSRGSLALQFFLVGGHRY
Human	481	LALGSDFSFTQIYQWDEGKQKRVROELAVQAPRAFCTYMPAGDAQLLAPSPFKGQTLVIR
Mouse	481	LALGSDFSFTQIYQWDEGKQKRVROELAVQAPRAFCTYMPAGDAQLLAPSPFKGQTLVIR
		P34
Human	541	HIVVDLSA 548 (SEQ ID NO:4)
Mouse	541	HVVVDLSA 548 (SEQ ID NO:3)

1

**COMPOSITION FOR PREVENTING,
TREATING OR ALLEVIATING DIABETES,
COMPRISING LGI3-DERIVED PEPTIDE AS
AN ACTIVE INGREDIENT**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a U.S. National Phase Application filed under 35 U.S.C. § 371 claiming benefit to International Patent Application No. PCT/KR2020/008879, filed Jul. 8, 2020, which claims the benefit of priority from Korean Patent Application No. 10-2019-0082713, filed Jul. 9, 2019, the contents of each of which are incorporated herein by reference in their entirety.

**REFERENCE TO A "SEQUENCE LISTING," A
TABLE, OR A COMPUTER PROGRAM LISTING
APPENDIX SUBMITTED AS AN ASCII TEXT
FILE**

The present application hereby incorporates by reference the entire contents of the text file named "206132-0124-00US_Sequence_Listing_ST25.txt" in ASCII format. The text file containing the Sequence Listing of the present application was created on Jan. 6, 2022 and is 10,654 bytes in size.

TECHNICAL FIELD

The present invention relates to a composition for preventing, treating or alleviating diabetes, which includes a leucine-rich repeat LGI family member 3 (LGI3)-derived peptide as an active ingredient.

BACKGROUND ART

Diabetes is caused by a decrease in pancreatic function, such as insulin secretion (type 1 diabetes) or insulin resistance of tissue (type 2 diabetes), and more than 90% cases of diabetes are caused by insulin resistance induced by accumulating an excessive energy source in fat cells and increasing an inflammatory response. According to the World Health Organization (WHO), the prevalence of diabetes in adults worldwide is about 9% and is increasing every year. Diabetes approximately doubles the risk of premature death, and the development of a therapeutic agent for diabetes, which is more effective and has less side effects, compared to the importance of various complications caused by diabetes, is the area with great unmet need. There is active competition around the world to develop a next-generation therapeutic agent for diabetes and enter the global market.

Currently, as a therapeutic agent for diabetes prescribed under FDA approval, insulin administered by injection or a pump is a representative therapeutic agent accounting for about 30% of the total therapeutic agents for diabetes, and other than this, an insulin sensitizer such as metformin or thiazolidinedione, an insulin secretagogue such as sulfonylurea, a peptide derivative such as a glucagon-like peptide-1 (GLP-1) derivative or a dipeptidyl peptidase-4 inhibitor, a renal glucose resorption inhibitor such as a sodium/glucose cotransporter 2 (SGLT2) inhibitor, and α -glucosidase inhibitor are used as a therapeutic agent for diabetes. Insulin has a limited effect on patients with type 1 diabetes who have decreased pancreatic insulin secretion and some patients with type 2 diabetes, and an insulin sensitizer has a limited

2

use in patients with renal failure or acute cardiovascular disease. An insulin secretagogue has a limited use in patients with gestational diabetes or type 1 diabetes, and has a problem of weight gain. A peptide derivative such as GLP-1 has relatively few side effects, but the risk of thyroid cancer and pancreatitis has been raised.

From the above, the unmet needs for therapeutic agents for diabetes having various side effects and limitations require the development of new concept next-generation therapeutic agents for diabetes. Existing oral therapeutic agents for diabetes cause various side effects such as hypoglycemia, weight gain, lactic acidosis, digestive tract disorders, cardiotoxicity and liver toxicity in long-term administration, and do not prevent pancreatic damage and the worsening of insulin resistance. Therefore, there is an urgent need to develop novel drugs which effectively regulate blood sugar without induction of hypoglycemia in long-term administration, and also have effects of pancreas protection, weight loss and improvement in insulin resistance. Recently, like examples of GLP-1 derivatives increased in use, as the clinical effectiveness and potential of peptide-based therapeutic agents for diabetes are high, it is very important to discover novel drug targets and mechanisms, develop peptide-based drugs, and develop a delivery optimization technique in the future.

Gene leucine rich repeat LGI family member 3 or leucine rich glioma inactivated 3 (LGI3) is located on human chromosome 8p21.3, deposited under NCBI Gene ID:203190, has an exon number of 8, and consists of 548 amino acids (NCBI Reference Sequence: NP_644807, SEQ ID NO: 4). In addition, LGI3 cDNA cloned from the brain cDNA library of a mouse (*Mus musculus*) consists of 2931 nucleotides, and consists of 548 amino acids (NCBI Reference Sequence: NP_660254.1, SEQ ID NO: 3) like a human. LGI3 is a protein with a molecular weight of about 60 kDa, having 548 amino acids, and it is difficult to apply LGI3 to the body as it is.

According to studies on LGI3 to date, the diabetes treatment effect of LGI3 by activity control is not known at all.

Based on the above problems, to use the control of LGI3 for diabetic treatment, the inventors discovered an LGI3-derived peptide suitable for application to the human body, and confirmed that the LGI3-derived peptide has an effect of treating and alleviating diabetes in animal models. Thus, the present invention was completed.

DISCLOSURE

Technical Problem

Technical problems to be achieved by the present invention are to provide a novel therapeutic composition that overcomes the side effects and limitations of existing therapeutic agents for diabetes, and at the same time, a composition for treating and alleviating both diabetes and complications caused thereby, and it was confirmed that the composition can be completed by including an LGI3-derived synthetic peptide capable of exhibiting the effect of treating and alleviating diabetes by control of physiological activity of adipokine LGI3.

Therefore, the present invention is directed to providing a pharmaceutical composition for preventing or treating diabetes, comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

The present invention is also directed to providing a food composition for preventing or alleviating diabetes, compris-

ing an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

The present invention is also directed to providing a pharmaceutical composition for preventing or alleviating one or more diabetes-associated metabolic disorders, comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

The present invention is also directed to providing a food composition for preventing or alleviating one or more diabetes-associated metabolic disorders, comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

However, technical problems to be solved in the present invention are not limited to the above-described problems, and other problems which are not described herein will be fully understood by those of ordinary skill in the art from the following descriptions.

Technical Solution

To solve the above-described problems, the present invention provides a pharmaceutical composition for preventing or treating diabetes, comprising an LGI3-derived peptide as an active ingredient.

The present invention also provides a food composition for preventing or alleviating diabetes, comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

The present invention also provides a method for preventing or treating diabetes, which includes administering an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 into a subject.

The present invention also provides a use of an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 for preparing a drug for preventing or treating diabetes.

The present invention also provides a use of an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 for preventing or treating diabetes.

According to one embodiment of the present invention, the diabetes may be one or more selected from the group consisting of type 1 diabetes, type 2 diabetes, and gestational diabetes.

According to another embodiment of the present invention, the composition may alleviate insulin resistance.

The present invention also provides a pharmaceutical composition for preventing or treating a diabetes-associated metabolic disorder, comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

The present invention also provides a food composition for preventing or alleviating a diabetes-associated metabolic disorder, comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

The present invention also provides a method for preventing or treating a diabetes-associated metabolic disorder, which includes administering an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 into a subject.

The present invention also provides a use of an LGI3-derived peptide, comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2, for preparing a drug for preventing or treating a diabetes-associated metabolic disorder.

The present invention also provides a use of an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 for preventing or treating a diabetes-associated metabolic disorder.

According to one embodiment of the present invention, the diabetes-derived metabolic disorder may be one or more phenomena selected from the group consisting of hyperglycemia, liver damage, pancreatic damage, and dyslipidemia.

Advantageous Effects

A composition comprising an LGI3-derived peptide as an active ingredient according to the present invention can prevent, treat or alleviate various types of metabolic disorders caused by diabetes by promoting reductions in body weight and blood sugar, which are main causes of diabetes and a diabetes-associated metabolic disorder, reducing pancreatic damage, improving a blood lipid composition and a liver function index, reducing blood insulin and improving insulin resistance.

In addition, the composition of the present invention induces improvements in blood sugar and insulin resistance without an anorectic action, and has an advantage of no or few side effects shown by conventional therapeutic agents for diabetes. Accordingly, the LGI3-derived peptide of the present invention and materials that can be developed by using it as a lead material are expected to be used in various aspects such as compositions for drugs, quasi-drugs, food additives, and fragrances and cosmetics for preventing and treating diabetes and related metabolic disorders thereof.

DESCRIPTION OF DRAWINGS

FIG. 1 is a graph confirming a weight loss in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 2 is a graph confirming that there is no change in feed intake in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 3 is a graph confirming that a blood sugar level is reduced in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 4A is a graph confirming that a pancreatic weight is increased in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 4B is a graph confirming that % weight based on a pancreatic weight is increased in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 5A is a micrograph of a pancreatic tissue section, showing that there is no change in pancreatic islets and the exocrine glands of the pancreas are enlarged in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 5B is a graph confirming a result of increasing zymogen granules of the pancreas in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 6A is a graph confirming changes in glycated hemoglobin (HbA1c) and total cholesterol (TCHOL), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), aspartate aminotransferase (AST), and alanine

aminotransferase (ALT) in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 6B is a graph confirming that a triglyceride/high density lipoprotein ratio (TG/HDL) and a low density lipoprotein/high density lipoprotein ratio (LDL/HDL) are reduced and improved in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 7A is a graph confirming that blood insulin is reduced and improved in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 7B is a graph confirming that an insulin resistance index (HOMA-IR, Homeostatic model assessment for insulin resistance) is reduced and improved in P25- and P34-administered db/db mice in comparison with an excipient-administered group.

FIG. 8 shows the comparison of amino acid sequences of human and mouse LGI3. The same amino acids in the two species are shown in gray, and the mouse LGI3 sequence corresponding to each of P25 and P34 peptide sequences is shown with a boxed line.

MODES OF THE INVENTION

The inventors studied a new therapeutic target for diabetes to overcome the side effects and limitations of existing therapeutic agents for diabetes. Accordingly, the inventors searched for and found a synthetic LGI3-derived peptide, and confirmed an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 has an effect of treating and improving diabetes and a diabetes-associated metabolic disorder through an animal test, and thus the present invention was completed.

Therefore, the present invention provides a pharmaceutical composition for preventing or treating diabetes or a diabetes-associated metabolic disorder, which includes an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient, and a food composition for preventing or alleviating diabetes or a diabetes-associated metabolic disorder, comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient.

In the specification, LGI3, which is an adipokine present only in vertebrates comprising humans, may include an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4. Here, the amino acid sequence of SEQ ID NO: 3 is an amino acid sequence of the LGI3 protein obtained from a mouse, and an amino acid sequence of SEQ ID NO: 4 is an amino acid sequence of the LGI3 protein obtained from a human. The mouse LGI3 amino acid sequence and the human amino acid sequence have 97% homology, and it is obvious that each LGI3-derived peptide can perform the same function in two species.

The "LGI3-derived peptide" used herein is a peptide having an amino acid sequence in a specific region, selected from the LGI3 protein comprising the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4, and the "peptide" used herein is a linear molecule formed by bonding amino acid residues by peptide bonds. The LGI3-derived peptide may be obtained by fragmenting the LGI3 protein, and may be prepared by a chemical synthesis method known in the art, particularly, a solid-phase synthesis technique or liquid synthesis technique.

The LGI3-derived peptide of the present invention may include one or more amino acid alterations in the range showing an effect of preventing, treating and alleviating diabetes.

In the LGI3-derived peptide of the present invention, modification of the N-terminus or the C-terminus may be induced to select a partial region of the amino acid sequence and increase the activity thereof. By such modification, the peptide of the present invention may have an increased half-life upon in-vivo administration.

To the N-terminus of the LGI3-derived peptide of the present invention, a protection group such as an acetyl group, a fluorenyl methoxy carbonyl group, a formyl group, a palmitoyl group, a myristyl group, a stearyl group and polyethylene glycol (PEG) may be bound, and the C-terminus of the peptide may be modified with a hydroxyl (—OH) group, an amino (—NH₂) group, or an azide (—NHNH₂). In addition, fatty acids, oligosaccharide chains, all of nanoparticles (gold particles, liposomes, heparin, hydrogel, etc.), amino acids, or carrier proteins may bind to an end of the peptide of the present invention or an R-group of an amino acid. The above-described amino acid modification may serve to improve the potency and stability of the peptide of the present invention. The term "stability" used herein means not only in vivo stability, but also storage stability (comprising storage stability at room temperature, and in a refrigerator or freezer).

The LGI3-derived peptide of the present invention preferably includes 3 to 30-mer amino acids, and more preferably, 5 to 15-mer amino acids, and as long as the peptide includes a sequence of consecutive amino acids based on any amino acid in the region of 361st to 375th amino acids, or 496th to 510th amino acids in the LGI3 protein sequence consisting of the amino acid sequence represented by SEQ ID NO: 3 or SEQ ID NO: 4, the length of the sequence is not limited. When the peptide is too long, there may be difficulty in application of the peptide, and when the peptide is too short, the function thereof may not be performed. The LGI3-derived peptide of the present invention may include an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2, or may consist of an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2, but the present invention is not limited thereto.

In diabetes, as apoptosis and tissue damage occur by autoimmune destruction of insulin-secreting beta cells in pancreatic islet cells or excessive hypertrophy and oxygen deprivation stress of visceral adipose cells, due to the residues of apoptosis, local inflammation is extended to systemic inflammation, causing insulin resistance in various tissues and leading to impairment of blood sugar control and various complications. In adipose tissue becoming the cause of diabetes in most cases, inflammatory adipokines showing increased secretion are various, such as TNF- α , IL-1, IL-6 and MCP-1, and an anti-inflammatory adipokine showing decreased secretion is adiponectin. Systemic chronic inflammation in diabetic patients induced by these adipokines is also called metabolic inflammation, and not only causes diabetes by reducing tissue sensitivity to insulin, but also disturbs metabolic homeostasis, causing dyslipidemia and various cardiovascular diseases.

Therefore, the inventors attempted to examine the effect of peptides controlling the activity of LGI3 in the LGI3-derived peptide group having an amino acid sequence of SEQ ID NO: 3 on diabetes.

According to an exemplary embodiment of the present invention, the LGI3 protein-derived peptide group having an amino acid sequence of SEQ ID NO: 3 was synthesized, and P25 (SEQ ID NO: 1) and P34 (SEQ ID NO: 2) peptides were selected to confirm the pharmacological effect of the LGI3-derived peptide. To this end, the P25 or P34 was administered to a diabetes animal model such as a db/db mouse, and

then a body weight was measured every week. As a result, it was confirmed that, compared to the excipient-administered group, in the P34-administered group, a weight loss effect was about 7%, and in the P25-administered group, there was no significant change in weight (see Example 1-2 and FIG. 1).

Meanwhile, there was no difference in feed intake in the P25 or P34 peptide-administered group, compared to the excipient-administered group, and it can be seen that the two peptides did not affect the brain appetite (see Example 1-2 and FIG. 2).

In addition, according to an exemplary embodiment of the present invention, the inventors measured blood sugar while the P25 or P34 peptide was administered into the db/db mouse for 6 weeks, confirming blood glucose decreasing effects of about 6 to 9% and about 6 to 11% in the P25-administered group and the P34-administered group, respectively. Both peptides showed a noticeable blood sugar decreasing effect (see Example 1-3 and FIG. 3).

In addition, according to an exemplary embodiment of the present invention, after the P25 or P34 peptide was administered to the db/db mouse for 6 weeks, its effect on the pancreas was investigated. As a result, compared to the excipient-administered group, in both of the P25-administered group and the P34-administered group, it can be confirmed that pancreatic weight increased, and by the P25 or P34 administration, the absolute weight of the pancreas increased about 9%, and the % body weight increased about 10% in the P25-administered group and about 17% in the P34-administered group (see Example 2-1, and FIGS. 4A and 4B).

In addition, according to one exemplary embodiment of the present invention, hematoxylin-eosin staining (H & E stain) performed for the histopathological examination of the pancreas showed a clear increase in the proportion of zymogen granules per unit area of the pancreatic exocrine (zymogen granules %/mm² of exocrine) (see Example 2-1, FIGS. 5A and 5B).

In addition, according to an exemplary embodiment of the present invention, after the P25 or P34 peptide was administered to the db/db mouse for 6 weeks, various blood biochemical indices were investigated. Compared to the excipient-administered group, in the P25-administered group and the P34-administered group, it was confirmed that triglyceride (TG), low density lipoprotein (LDL), AST and ALT decreased, and high density lipoprotein (HDL) increased (see Example 2-2 and FIG. 6A). In addition, compared to the excipient-administered group, in the P25-administered group and the P34-administered group, it can be confirmed that a TG/HDL ratio and an LDL/HDL ratio, which are indices of blood lipids, are remarkably reduced and improved (see Example 2-2 and FIG. 6B).

In addition, according to an exemplary embodiment of the present invention, as a result of investigating a blood insulin and insulin resistance index (HOMA-IR) after the P25 or P34 peptide was administered to the db/db mouse for 6 weeks, compared to the excipient-administered group, in the P25-administered group and the P34-administered group, it was confirmed that the HOMA-IR is reduced and improved (see Example 2-3, FIGS. 7A and 7B).

From the above result, the inventors confirmed that the LGI3-derived peptides P25 and P34 reduce blood sugar and improve the insulin resistance index, exhibiting an effect of preventing or treating diabetes, and an effect of improving a diabetes-associated metabolic disorder such as pancreatic damage, dyslipidemia, and liver damage.

In addition, both of the P25 and P34 peptides have suitable sizes for application to the human body, exhibit high solubility in water (P25, 10 mg/ml; P34, 1 mg/ml), and thus facilitate formulation and administration.

Unlike existing therapeutic agents for diabetes, the composition comprising an LGI3-derived peptide according to the present invention exhibits an effect of improving indicators of diabetes and diabetes-associated metabolic disorders by controlling the activity of LGI3, which is an adipokine secreted from adipose tissue. Therefore, it can be used as a novel (first-in-class) therapeutic agent for diabetes based on LGI3, which overcomes the side effects and limitations shown from existing drugs or a lead material for development of a therapeutic agent, and can be used for health functional foods for modern people whose diets causing metabolic diseases are prevalent.

In addition, since the effect of losing weight and improving indicators of diabetes by administration of an LGI3-derived peptide was confirmed, it is assumed that metabolic disorders related to diabetes can be alleviated due to the increases in adipose cell differentiation and insulin sensitivity by controlling LGI3's functions of inhibiting the differentiation of adipose cells and controlling metabolic inflammation, and the functional improvement in subcutaneous fat and the reduction in visceral and liver fats through absorption of blood glucose and increased fat storage capacity. That is, in diabetic patients, the composition comprising an LGI3-derived peptide according to the present invention generally treats diabetes through recovery from accumulation of excessive adipose tissue, deficient differentiation capacity of adipose cells and increased metabolic inflammation, and is differentiated from existing anti-diabetic substances.

Collectively, the LGI3-derived peptide of the present invention can be used in a pharmaceutical composition for preventing or treating diabetes, and used as a lead material for the development of a therapeutic agent for diabetes. In addition, the LGI3-derived peptide of the present invention may be used in a food composition for preventing or alleviating diabetes, and pancreatic and liver damage and dyslipidemia, induced by diabetes.

The LGI3-derived peptide of the present invention may be included at 1 pg to 30 g w/v % in a composition for preventing, treating or alleviating diabetes and a diabetes-associated metabolic disorder, but the present invention is not limited thereto.

In addition, the present invention may provide a method of preventing, treating or alleviating diabetes or a diabetes-associated metabolic disorder, which includes administering a composition comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient into a subject.

The term "administration" used herein refers to introduction of a pharmaceutical composition of the present invention by any appropriate method to a patient, and the administration route of the composition of the present invention may be various, for example, oral or parenteral, as long as the composition of the present invention can reach target tissue.

The term "subject" used herein refers to a target into which the LGI3-derived peptide of the present invention, or a pharmaceutical composition comprising the same can be administered, and there is no limit to a target. The subject used herein is preferably a mammal including a human, for example, a mammal such as a human, a mouse, a rat, a monkey, a cat, a dog, a cow or a pig, but the present invention is not limited thereto.

The “prevention” used herein refers to all actions of delaying the hypertrophy of adipose tissue or a metabolic disorder thereby by the administration of the composition of the present invention, the “treatment” used herein refers to all actions involved in alleviating or beneficially changing symptoms of diabetes or a metabolic disorder thereby by the administration of the pharmaceutical composition according to the present invention, and the “alleviation” means all actions that reduce parameters associated with diabetes or a metabolic disorder induced by a high fat diet, for example, the degree of symptoms, by the administration of the composition according to the present invention.

The “diabetes” used herein is a metabolic disorder syndrome characterized by the lack of insulin hormone produced from the beta cells of the pancreas or insulin resistance, and further hyperglycemia resulting from the deficiency of both. The diabetes may be classified into insulin-dependent diabetes (IDDM, type 1) and non-insulin-dependent diabetes (NIDDM, type 2) caused by impairment of insulin resistance and insulin secretion. In both type 1 and type 2 diabetes, various complications such as a heart disease, an intestinal disease, an eye disease, a kidney disease, a neurological disease, and stroke occur, leading to chronic neurological diseases and cardiovascular diseases due to long-term increased blood sugar and insulin levels, and acute complications due to short-term hypoglycemia and hyperglycemia. Diabetes causes chronic hyperglycemia, and also causes disorders of lipid and protein metabolism as well as carbohydrate metabolism. The conditions are diverse, and are directly caused by hyperglycemia, and include diabetic peripheral neuropathy, diabetic retinopathy, diabetic nephropathy, diabetic cataract and keratosis, diabetic arteriosclerosis in the retina, kidneys, nerves and cardiovascular system.

The “diabetes-associated metabolic disorder” used herein refers to symptoms resulting from hyperglycemia resulting from, caused, derived, or associated with diabetes and disorders of lipid or protein metabolism, and usually, is the generic term for hyperglycemia, pancreatic and liver damage, caused by disorders of glucose and lipid metabolism. More specifically, the “pancreatic and liver disease” refers to a failure of the pancreas or liver to function due to extrinsic or intrinsic factors, and the “blood lipid abnormality” used herein means that an increase in total blood cholesterol, low density lipoprotein-cholesterol, or a triglyceride, or a decrease in high density lipoprotein-cholesterol, compared to a normal condition. That is, the diabetes-associated metabolic disorders may be, but are not limited to, one or more phenomena selected from the group consisting of hyperglycemia, liver damage, pancreatic damage and dyslipidemia, and the pancreatic damage may include pancreatic exocrine hypothyroidism.

The pharmaceutical composition according to the present invention may further include a suitable carrier, excipient and diluent, which are conventionally used in preparation of a pharmaceutical composition.

The “carrier” used herein is also called a vehicle, referring to a compound facilitating the addition of a protein or peptide into cells or tissue. For example, dimethyl sulfoxide (DMSO) is a carrier generally used to make more organic materials enter cells or tissue of an organism.

The “diluent” used herein is defined as a compound which not only stabilizes the biologically active form of a target protein or peptide, but also dilutes the protein or peptide in water. Salts dissolved in a buffer solution are used as diluents in the art. A conventionally used buffer solution is phosphate buffered saline, which is because it mimics a salt

state of human body fluid. Since the buffered salt can control the pH of a solution at a low concentration, it is rare for a buffer diluent to change the biological activity of a compound. Compounds containing azelaic acid, used herein, are pharmaceutical compositions, which may be administered alone, or administered after being mixed with other ingredients or suitable carriers or excipients as in combination therapy.

In addition, the pharmaceutical composition for preventing or treating diabetes, comprising the LGI3-derived peptide as an active ingredient, according to the present invention may be used in the form of a powder, a granule, a tablet, a capsule, a suspension, an emulsion, a syrup, a preparation for external use such as an aerosol, or a sterilized injectable solution according to a conventional method, and the carrier, excipient and diluent which may be included in the pharmaceutical composition according to the present invention may include lactose, dextrose, sucrose, an oligosaccharide, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia gum, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinyl pyrrolidone, water, methyl hydroxybenzoate, propyl hydroxybenzoate, talc, magnesium stearate and mineral oil. In formulation, generally used diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrants and surfactants are used. A solid formulation for oral administration may be a tablet, pill, powder, granule or capsule, and such a solid formulation may be prepared by mixing at least one of excipients, for example, starch, calcium carbonate, sucrose, lactose and gelatin, with the active ingredient. Also, in addition to the simple excipient, lubricants such as magnesium stearate and talc may also be used. As a liquid formulation for oral administration, a suspension, a liquid for internal use, an emulsion, or a syrup may be used, and a generally-used simple diluent such as water or liquid paraffin, as well as various types of excipients, for example, a wetting agent, a sweetener, a fragrance and a preservative may be included. A formulation for parenteral administration may be a sterilized aqueous solution, a non-aqueous solvent, a suspension, an emulsion, a lyophilized preparation or a suppository. As the non-aqueous solvent or suspension, propylene glycol, polyethylene glycol, a vegetable oil such as olive oil, or an injectable ester such as ethyl oleate may be used. As a suppository base, Witepsol, Tween 61, cacao butter, laurinum, or glycerogelatin may be used.

The pharmaceutical composition of the present invention may be administered orally or parenterally, preferably, parenterally, and in the case of parenteral administration, muscular injection, intravenous injection, subcutaneous injection, intraperitoneal injection, local administration or transdermal administration may be used.

A suitable dose of the pharmaceutical composition of the present invention may vary depending on factors such as a formulation method, an administration method, a patient’s age, weight or gender, a pathological condition, a diet, administration time, an administration route, an excretion rate and reaction sensitivity.

The pharmaceutical composition of the present invention may be prepared in the form of a unit dose or in a large-capacity container by formulation with a pharmaceutically acceptable carrier and/or excipient according to a method easily performed by those of ordinary skill in the art to which the invention belongs. Here, the pharmaceutical composition of the present invention may be formed in the form of a solution, suspension or emulsion in an oil or

aqueous medium, an extract, a powder, a granule, a tablet or a capsule, and may further include a suspending agent or a stabilizer.

Moreover, the present invention provides a food composition comprising an LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 as an active ingredient. In addition, the LGI3-derived peptide comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 may be added to foods for alleviating symptoms of diabetes or a diabetes-associated metabolic disorder. In the present invention, foods include all functional foods including functional foods and health functional foods. When the LGI3-derived peptide of the present invention is used as a food additive, the LGI3-derived peptide may be used alone or in combination with another food or food ingredient, and may be suitably used by a conventional method. The mixing amount of the active ingredient may be appropriately determined according to the purpose of use (prevention, health or therapeutic treatment). Generally, in production of foods or beverages, the LGI3-derived peptide of the present invention may be added at 15 wt % or less, and preferably 10 wt % or less with respect to the raw materials. However, in long-term consumption for health and hygiene or health control, the amount of the composition may be the same as or lower than the above-mentioned range.

There is no particular limit to the type of food. Examples of the foods to which the above-described materials can be added include meat, sausage, bread, chocolate, candy, snack, confectionery, pizza, ramen, other noodles, gum, dairy products including ice cream, various soups, beverages, tea, drinks, alcoholic beverages and a vitamin complex, and in an ordinary sense, all health functional foods are included.

The health beverage composition according to the present invention may contain various flavoring agents or natural carbohydrates as additional ingredients, like a common beverage. include conventional sugars, for example, monosaccharides such as glucose, fructose, etc.; disaccharides such as maltose, sucrose, etc.; and polysaccharides such as dextrin, cyclodextrin, etc., and sugar alcohols such as xylitol, sorbitol, erythritol, etc. As a sweetener, natural sweeteners such as thaumatin and a stevia extract, or a synthetic sweetener such as saccharin or aspartame may be used. The proportion of the natural carbohydrate is generally about 0.01 to 0.20 g, and preferably, about 0.04 to 0.10 g per 100 mL of the composition of the present invention.

In addition, the composition of the present invention may contain various nutrients, vitamins, electrolytes, flavoring agents, pectic acid and a salt thereof, alginic acid and a salt thereof, organic acids, protective colloidal thickening agents, pH adjustors, stabilizers, preservatives, glycerin, alcohols, or carbonizing agents used in carbonated beverages. Other than these, the composition of the present invention may contain fruit pulp for producing natural fruit juices, fruit drinks and vegetable drinks. The proportions of these additives are not critical, but are generally selected in the range of 0.01 to -0.20 parts by weight with respect to 100 parts by weight of the composition of the present invention.

In addition, the present invention provides a use of an LGI3-derived peptide, comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 for preparing a drug for preventing or treating diabetes.

In addition, the present invention provides a use of the LGI3-derived peptide, comprising an amino acid sequence represented by SEQ ID NO: 1 or SEQ ID NO: 2 for

preparing a drug for preventing or treating a diabetes-associated metabolic disorder.

As the present invention may have various modifications and embodiments, specific embodiments the present invention will be described in further detail below. However, the present invention is not limited to the specific embodiments, and it should be understood that the present invention includes all modifications, equivalents and alternatives included in the technical idea and scope of the present invention. To explain the present invention, if it is determined that a detailed description of the related art may obscure the gist of the present invention, the detailed description thereof will be omitted.

Hereinafter, to help in understanding the present invention, exemplary examples will be suggested. However, the following examples are merely provided to more easily understand the present invention, and not to limit the present invention.

EXAMPLES

Example 1. Confirmation of Effect of LGI3-Derived Peptide on Weight, Feed Intake and Blood Sugar in Diabetic Animal Model

Example 1-1. Preparation of Diabetic Animal Models and Administration of Test Materials

As laboratory animals, specific pathogen-free (SPF) db/db mice (C57BLKS/J-db/dbC57BL/6i, male, Central Lab. Animal Inc., Korea) were used. The animals were fed under a temperature of $23\pm 3^{\circ}$ C., a relative humidity of $55\pm 15\%$, with a ventilation frequency of 10 to 20 times/hr, 12-hour lighting and an illuminance of 150 to 300 Lux. As feed, solid feed for rodents (Teklad certified irradiated global 18% protein rodent diet; 2918C, ENVIGO, UK) was provided ad libitum.

The laboratory animals were weighed for ranking and randomly allocated to the following groups such that an average weight of each group was distributed as evenly as possible according to the ranked weights: an excipient (vehicle)-administered group (phosphate buffered saline as an excipient, Welgene, Korea) as a control, a P25 (SEQ ID NO: 1)-administered group, and a P34 (SEQ ID NO: 2)-administered group. There were 8 animals per group. The LGI3-derived peptide was administered intraperitoneally once/day, twice/week, and a total of 12 times for 6 weeks. A dose of the LGI3-derived peptide was 10 mg/kg, and a dosage thereof was 10 ml/kg/day.

After the administration of the LGI3-derived peptide, types of general symptoms and the severity of symptoms were observed once a day, and as a result of observation of general symptoms during the test period, no abnormal symptoms or dead animals were observed in all groups. The animals were weighed at the time of acquisition, group division, the initiation of administration and autopsy, and at other times, weighed once a week. An amount of feed intake was measured once a week during the administration period. For blood glucose measurement, the animals were fasted (water provided) for about 6 hours before the measurement. Blood glucose was measured using a blood glucose meter (G-Doctor, Green Cross) on the measurement day, and measured once a week.

Example 1-2. Confirmation of Effect of Administration of LGI3-Derived Peptide on Weight and Appetite

To confirm the effect of the P25 or P34 administered into the db/db mice in Example 1-1 on weight and appetite, a weekly weight and feed intake were checked.

13

As a result, as shown in FIG. 1, a weight loss effect was confirmed in the P34-administered group. More specifically, an approximate 6 to 7% weight loss was confirmed at week 5 to 7 in the P34-administered group.

On the other hand, as confirmed in FIG. 2, there was no feed intake difference in the P25- and P34-administered groups, compared to the excipient-administered group. This result indicates that in the P25- or P34-administered group, there is no effect on the appetite of the individual, and a weight increase is inhibited in the P34-administered group.

Example 1-3. Confirmation of Effect on Blood
Glucose by Administration of LGI3-Derived
Peptide

To confirm the effect of the P25 or P34 administered into the db/db mice in Example 1-1 on blood sugar, blood sugar was measured by the method described in Example 1-1.

As a result, as shown in FIG. 3, it can be confirmed that an approximate 6 to 9% decrease in blood glucose was shown at week 1 to 5 in the P25-administered group, and an approximate 7 to 11% decrease in blood glucose was shown at week 1 to 5 in the P34-administered group.

Example 2. Confirmation of Effect of
LGI3-Derived Peptide on Pancreas, Indices in
Blood, and Insulin Resistance in Diabetic Animal
Model

Example 2-1. Confirmation of Pancreatic Weight
and Histopathological Change by Administration of
LGI3-Derived Peptide

Autopsy was performed to confirm the effect of the P25 or P34 administered into the db/db mice in Example 1-1 on the pancreas. The animals were fasted (water provided) for about 16 hours before autopsy. At the time of autopsy, the animals were anesthetized by inhalation with isoflurane, followed by laparotomy and blood collection from the posterior vena cava. After the blood collection, the abdominal aorta and posterior vena cava of the animal were cut, and the pancreas was removed from the animal, which had been exsanguinated, followed by weighing and fixation in a 10% neutral buffered formalin solution. The fixed pancreas was stained by H&E staining, and a pancreatic islet number, islets of pancreatic tissue/cm² and the diameter of the pancreatic islet (μm), and the proportion of zymogen granules per unit area of the pancreatic exocrine (zymogen granules %/mm² of exocrine) were analyzed, and image analysis was performed using an image analysis program (iSolution EL ver 9.1, IMT i-solution Inc., Quebec, Canada).

As a result, as shown in FIG. 4A, an approximate 9% increase in pancreatic weight was confirmed in the P25- and P34-administered groups, compared to the excipient-administered group.

As shown in FIG. 4B, approximate 10% and 17% increases in % pancreatic weight relative to body weight were confirmed in the P25- and P34-administered groups, respectively.

As a result of histopathological examination, as shown in FIGS. 5A and 5B, compared to the excipient-administered group, changes in pancreatic islet numbers (islets/cm²) and diameters (μm) in the P25-administered group and P34-administered group were not observed, and significant increases in the proportion of zymogen granules per unit

14

area of the pancreatic exocrine (zymogen granules %/mm² of exocrine) were observed in the P25- and P34-administered groups.

These results show that P25 and P34 have therapeutic and alleviating effects on pancreatic exocrine insufficiency generated in diabetes.

Example 2-2. Confirmation of Effect on Indices in
Blood by Administration of LGI3-Derived Peptide

To confirm the effect of the P25 or P34 administered into the db/db mice in Example 1-1 on indices in blood, glycated hemoglobin (HbA1c) and total cholesterol (TCHOL), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured, and the TG/HDL ratio and the LDL/HDL ratio were calculated.

As a result, as shown in FIG. 6A, it can be confirmed that the blood TG, LDL, AST and ALT were reduced in both of the P25-administered group and the P34-administered group, compared to the excipient-administered group, showing that a blood lipid improving effect and a liver function protecting effect can be achieved by P25 or P34 administration.

In addition, as shown in FIG. 6B, it can be confirmed that the TG/HDL ratio and the LDL/HDL ratio were reduced in both of the P25-administered group and the P34-administered group, showing that the blood lipid improving effect can be achieved by P25 or P34 administration.

Example 2-3. Confirmation of Effect on Insulin
Resistance Index by Administration of
LGI3-Derived Peptide

To confirm the effect of the P25 or P34 administered into the db/db mice in Example 1-1 on the insulin resistance index, serum insulin was quantitatively analyzed using an ELISA kit (Shibayagi, AKRIN-011T). An insulin resistance index (HOMA-IR=[fasting insulin (μIU/mL)×fasting blood glucose (mmol/L)]/22.5) was calculated from the insulin concentration and blood sugar level, which had been quantitatively analyzed.

As a result, as shown in FIG. 7A, it was confirmed that the blood insulin levels were reduced and improved in both of the P25-administered group and the P34-administered group, compared to the excipient-administered group, and as shown in FIG. 7B, the insulin resistance index (HOMA-IR) was reduced and improved in the P25-administered group and the P34-administered group, compared to the control.

Collectively, the inventors confirmed that the LGI3-derived peptides, P25 (QNGFYSHQALHAWHR, SEQ ID NO: 1) and P34 (DEGRQKFVRFQELAV, SEQ ID NO: 2), have a diabetes treatment and alleviation effect in the db/db mice. Particularly, as the P34 peptide showed a weight loss effect, and the P25 and P34 peptides showed not only blood sugar and insulin resistance index improvement effects, but also showed effects of treating and improving diabetes-associated symptoms, such as pancreatic damage and blood lipids (triglycerides, LDL and HDL) and abnormal liver functions (AST and ALT), it can be seen that the P24 and P34, which are LGI3-derived peptides controlling LGI3 activity, can be used in drugs and health functional foods for preventing, treating or alleviating diabetes and a diabetes-associated metabolic disorder and lead materials for developing the same.

It should be understood by those of ordinary skill in the art that the above description of the present invention is

15

exemplary, and the exemplary embodiments disclosed herein can be easily modified into other specific forms without departing from the technical spirit or essential features of the present invention. Therefore, the exemplary embodiments described above should be interpreted as illustrative and not limited in any aspect.

INDUSTRIAL APPLICABILITY

A composition comprising an LGI3-derived peptide as an active ingredient according to the present invention may prevent, treat or alleviate various types of metabolic disorders caused by diabetes by promoting reductions in body weight and blood sugar, which are main causes of diabetes and a diabetes-associated metabolic disorder, reducing pan-

16

creatic damage, improving a blood lipid composition and a liver function index, reducing blood insulin and improving insulin resistance.

In addition, the composition of the present invention induces improvements in blood sugar and insulin resistance without an anorectic action, and has an advantage of no or few side effects shown by conventional therapeutic agents for diabetes. Accordingly, the LGI3-derived peptide of the present invention and materials that can be developed by using it as a lead material are expected to be used in various aspects such as compositions for drugs, quasi-drugs, food additives, and fragrances and cosmetics for preventing and treating diabetes and related metabolic disorders thereof, and thus has industrial applicability.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 4

<210> SEQ ID NO 1

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: LGI3 derived peptide 25

<400> SEQUENCE: 1

Gln Asn Gly Phe Tyr Ser His Gln Ala Leu His Ala Trp His Arg
1 5 10 15

<210> SEQ ID NO 2

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: LGI3 derived peptide 34

<400> SEQUENCE: 2

Asp Glu Gly Arg Gln Lys Phe Val Arg Phe Gln Glu Leu Ala Val
1 5 10 15

<210> SEQ ID NO 3

<211> LENGTH: 548

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: leucine-rich repeat LGI family member 3 precursor [Mus musculus] NP_660254.1

<400> SEQUENCE: 3

Met Ala Gly Leu Arg Ala Arg Arg Gly Pro Gly Arg Arg Leu Leu Val
1 5 10 15

Leu Ser Thr Leu Gly Phe Cys Leu Met Leu Gln Val Ser Ala Lys Arg
20 25 30

Pro Pro Lys Thr Pro Pro Cys Pro Pro Ser Cys Ser Cys Thr Arg Asp
35 40 45

Thr Ala Phe Cys Val Asp Ser Lys Ser Val Pro Lys Asn Leu Pro Ser
50 55 60

Glu Val Ile Ser Leu Thr Leu Val Asn Ala Ala Phe Ser Glu Ile Gln
65 70 75 80

Asp Gly Ala Phe Ser His Leu Pro Leu Leu Gln Phe Leu Leu Leu Asn
85 90 95

Ser Asn Lys Phe Thr Leu Ile Gly Asp Asn Ala Phe Ile Gly Leu Ser
100 105 110

His	Leu	Gln	Tyr	Leu	Phe	Ile	Glu	Asn	Asn	Asp	Ile	Trp	Ala	Leu	Ser
		115					120					125			
Lys	Phe	Thr	Phe	Arg	Gly	Leu	Lys	Ser	Leu	Thr	His	Leu	Ser	Leu	Ala
	130					135					140				
Asn	Asn	Asn	Leu	Gln	Thr	Leu	Pro	Arg	Asp	Ile	Phe	Arg	Pro	Leu	Asp
145					150					155					160
Ile	Leu	Ser	Asp	Leu	Asp	Leu	Arg	Gly	Asn	Ala	Leu	Asn	Cys	Asp	Cys
				165					170					175	
Lys	Val	Lys	Trp	Leu	Val	Glu	Trp	Leu	Ala	His	Thr	Asn	Thr	Thr	Val
			180					185						190	
Ala	Pro	Ile	Tyr	Cys	Ala	Ser	Pro	Pro	Arg	Phe	Gln	Glu	His	Lys	Val
		195					200					205			
Gln	Asp	Leu	Pro	Leu	Arg	Glu	Phe	Asp	Cys	Ile	Thr	Thr	Asp	Phe	Val
	210					215					220				
Leu	Tyr	Gln	Thr	Leu	Ser	Phe	Pro	Ala	Val	Ser	Ala	Glu	Pro	Phe	Leu
225					230					235					240
Tyr	Ser	Ser	Asp	Leu	Tyr	Leu	Ala	Leu	Ala	Gln	Pro	Gly	Ala	Ser	Ala
				245				250						255	
Cys	Thr	Ile	Leu	Lys	Trp	Asp	Tyr	Val	Glu	Arg	Gln	Leu	Arg	Asp	Tyr
			260					265					270		
Asp	Arg	Ile	Pro	Ala	Pro	Ser	Ala	Val	His	Cys	Lys	Pro	Met	Val	Val
		275					280					285			
Asp	Gly	Gln	Leu	Tyr	Val	Val	Val	Ala	Gln	Leu	Phe	Gly	Gly	Ser	Tyr
	290					295					300				
Ile	Tyr	His	Trp	Asp	Pro	Asn	Thr	Thr	Arg	Phe	Thr	Lys	Leu	Gln	Asp
305					310					315					320
Ile	Asp	Pro	Gln	Arg	Val	Arg	Lys	Pro	Asn	Asp	Leu	Glu	Ala	Phe	Arg
				325					330					335	
Ile	Asp	Gly	Asp	Trp	Phe	Phe	Ala	Val	Ala	Asp	Ser	Ser	Lys	Ala	Gly
			340					345					350		
Ala	Thr	Ser	Leu	Tyr	Arg	Trp	His	Gln	Asn	Gly	Phe	Tyr	Ser	His	Gln
		355					360					365			
Ala	Leu	His	Ala	Trp	His	Arg	Asp	Thr	Asp	Leu	Glu	Phe	Val	Asp	Gly
	370					375					380				
Glu	Gly	Lys	Pro	Arg	Leu	Ile	Val	Ser	Ser	Ser	Ser	Gln	Ala	Pro	Val
385					390					395					400
Ile	Tyr	Gln	Trp	Ser	Arg	Ser	Gln	Lys	Gln	Phe	Val	Ala	Gln	Gly	Glu
				405					410					415	
Val	Thr	Gln	Val	Pro	Asp	Ala	Gln	Ala	Val	Lys	His	Phe	Arg	Ala	Gly
			420					425				430			
Arg	Asp	Ser	Tyr	Leu	Cys	Leu	Ser	Arg	Tyr	Ile	Gly	Asp	Ser	Lys	Ile
		435					440					445			
Leu	Arg	Trp	Glu	Gly	Thr	Arg	Phe	Ser	Glu	Val	Gln	Ala	Leu	Pro	Ser
	450					455					460				

-continued

530	535	540
Asp Leu Ser Ala		
545		
<210> SEQ ID NO 4		
<211> LENGTH: 548		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: leucine-rich repeat LGI family member 3		
precursor [Homo sapiens] NP_644807.1		
<400> SEQUENCE: 4		
Met Ala Gly Leu Arg Ala Arg Gly Gly Pro Gly Pro Gly Leu Leu Ala		
1 5 10 15		
Leu Ser Ala Leu Gly Phe Cys Leu Met Leu Gln Val Ser Ala Lys Arg		
20 25 30		
Pro Pro Lys Thr Pro Pro Cys Pro Pro Ser Cys Ser Cys Thr Arg Asp		
35 40 45		
Thr Ala Phe Cys Val Asp Ser Lys Ala Val Pro Arg Asn Leu Pro Ser		
50 55 60		
Glu Val Ile Ser Leu Thr Leu Val Asn Ala Ala Phe Ser Glu Ile Gln		
65 70 75 80		
Asp Gly Ala Phe Ser His Leu Pro Leu Leu Gln Phe Leu Leu Leu Asn		
85 90 95		
Ser Asn Lys Phe Thr Leu Ile Gly Asp Asn Ala Phe Thr Gly Leu Ser		
100 105 110		
His Leu Gln Tyr Leu Phe Ile Glu Asn Asn Asp Ile Trp Ala Leu Ser		
115 120 125		
Lys Phe Thr Phe Arg Gly Leu Lys Ser Leu Thr His Leu Ser Leu Ala		
130 135 140		
Asn Asn Asn Leu Gln Thr Leu Pro Arg Asp Ile Phe Arg Pro Leu Asp		
145 150 155 160		
Ile Leu Asn Asp Leu Asp Leu Arg Gly Asn Ser Leu Asn Cys Asp Cys		
165 170 175		
Lys Val Lys Trp Leu Val Glu Trp Leu Ala His Thr Asn Thr Thr Val		
180 185 190		
Ala Pro Ile Tyr Cys Ala Ser Pro Pro Arg Phe Gln Glu His Lys Val		
195 200 205		
Gln Asp Leu Pro Leu Arg Glu Phe Asp Cys Ile Thr Thr Asp Phe Val		
210 215 220		
Leu Tyr Gln Thr Leu Ala Phe Pro Ala Val Ser Ala Glu Pro Phe Leu		
225 230 235 240		
Tyr Ser Ser Asp Leu Tyr Leu Ala Leu Ala Gln Pro Gly Val Ser Ala		
245 250 255		
Cys Thr Ile Leu Lys Trp Asp Tyr Val Glu Arg Gln Leu Arg Asp Tyr		
260 265 270		
Asp Arg Ile Pro Ala Pro Ser Ala Val His Cys Lys Pro Met Val Val		
275 280 285		
Asp Ser Gln Leu Tyr Val Val Val Ala Gln Leu Phe Gly Gly Ser Tyr		
290 295 300		
Ile Tyr His Trp Asp Pro Asn Thr Thr Arg Phe Thr Arg Leu Gln Asp		
305 310 315 320		
Ile Asp Pro Gln Arg Val Arg Lys Pro Asn Asp Leu Glu Ala Phe Arg		
325 330 335		

