Treatment and Prevention of Obesity Using a Combination of Mitochondrial Uncouplers and Glucagon-Like Peptide-1 Receptor Agonists

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/566,862, filed on 18 March 2024, which is hereby incorporated by reference in its entirety.

BACKGROUND

Glucagon-like peptide-1 (GLP-1) is a hormone that the human body naturally produces. It's involved in several biological processes connected to food digestion and can reduce hunger,
increasing feelings of fullness by delaying the emptying of the stomach. Molecules, simulating GLP-1 activity (GLP-1 agonists) act by binding to GLP-1 receptors, resulting in the same effects. As a result, multiple GLP-1 receptor agonists have been developed and are being developed for treatment of obesity. Several clinical studies of GLP-1 agonists have demonstrated approximately 15-20% weight loss in human subjects.

Mitochondrial proton cycling is responsible for a significant proportion of basal or standard metabolic rate. Energy expenditure can be increased by stimulating the activity of uncoupling protein 1 (UCP1) in brown adipocytes either directly or through beta 3-adrenoceptor agonists. UCP2 in a number of tissues, UCP3 in skeletal muscle, and the adenine nucleotide translocase have also been proposed as possible drug targets.

SUMMARY

The present technology provides methods, compositions, and kits for enhancing weight loss, or preventing or treating obesity or other conditions related thereto, such as diabetes. A GLP-1 agonist is administered together with, or prior to, a mitochondrial uncoupler. Use of the uncoupler increases weight loss and enhances treatment of obesity and obesity-related medical conditions, such as by preventing weight regain after cessation of administration of the GLP-1 agonist.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A shows the time course of weight loss in obese mice with administration of GLP-1 receptor agonist liraglutide at two different doses, and for comparison with the administration

of mitochondrial uncoupler SkQ1 together with liraglutide. SkQ1 enhanced the weight loss induced by liraglutide. Fig. 1B shows the cumulative food intake for the experiment shown in Fig. 1A. The mitochondrial uncoupler had little effect on food intake.

Fig. 2A shows the time course of weight regain after stopping GLP-1 agonist treatment. Liraglutide was administered on days 1-20 and then replaced with vehicle injection for days 21-24, while SkQ1 was administered on days 1-24. SkQ1 prevented weight regain after stopping liraglutide treatment. Fig. 2B shows the cumulative food intake over days 21-24 for each condition in the experiment depicted in Fig. 2A.

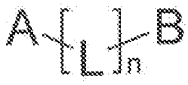
Figs. 3A and 3B show the results obtained from an experiment similar to that shown in Figs. 2A and 2B, but using a higher dose of SkQ1.

Figs. 4A and 4B show the results obtained from an experiment similar to that shown in Figs. 1A and 1B, but comparing two different doses of SkQ1.

DESCRIPTION

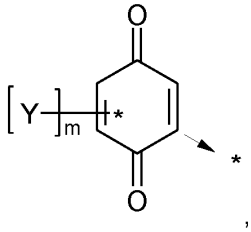
The present technology provides methods and compositions to aid in treating and preventing obesity as well as obesity-associated diseases, such as (but not limited to) non-alcoholic fatty liver disease, non-alcoholic steatohepatitis (NASH) and metabolic dysfunction-associated steatohepatitis (MASH).

An aspect of the present technology is a method to aid in treatment and/or prevention of obesity and/or obesity-associated diseases. The method includes administering to a patient in need thereof a therapeutically or prophylactically effective amounts of a GLP-1 agonist and (simultaneously, sequentially or sequentially with a temporary overlap) a mitochondria uncoupler. In one embodiment of the invention the mitochondrial uncoupler is a compound of Formula I:



Formula I

wherein A is hydrogen or an effector moiety, which is an antioxidant optionally having a following structure:



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and/or reduced forms thereof,

wherein m is from 0 to 3; each Y is independently selected from the group consisting of: lower alkyl (1 to 6 carbons), lower alkoxy (1 to 6 carbons);

L is a linker group, comprising:

a) straight or branched hydrocarbon chain which can be optionally substituted by one or more substituents and optionally contains one or more double or triple bonds;

b) a natural isoprene chain;

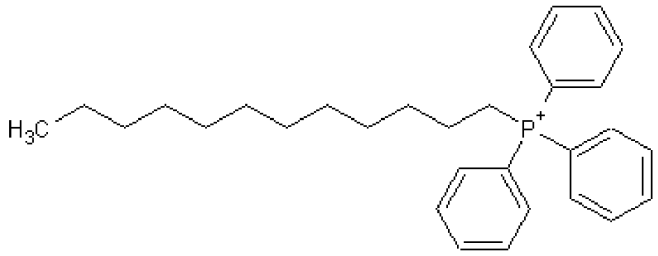
n is the number of carbon atoms in the linker, which is an integer from 1 to 40; and

B is a mitochondria targeting group comprising a lipophilic cation;

and a pharmacologically acceptable anion;

and/or solvates, salts, isomers, or prodrugs thereof.

The set of compounds of Formula I includes C_nTPP compunds, wherein n is from 5 to 12. For example C12TPP:



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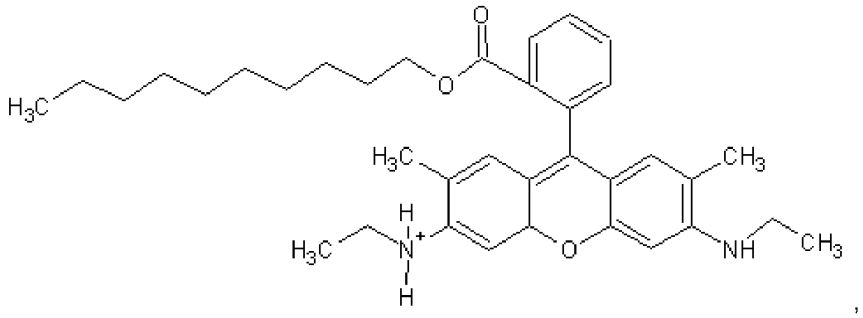
or C_nR1 (wherein n is from 4 to 12), for example C10R1:



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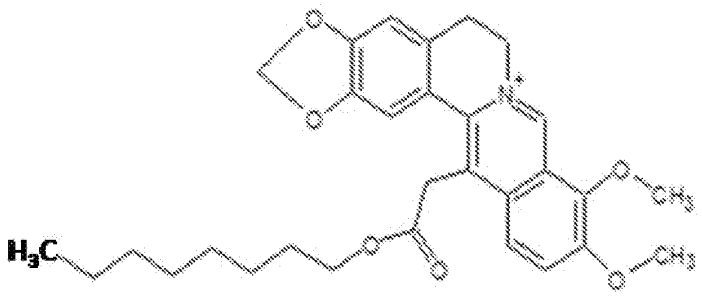
C_nBerb (wherein n is from 4 to 12), for example C8Berb:



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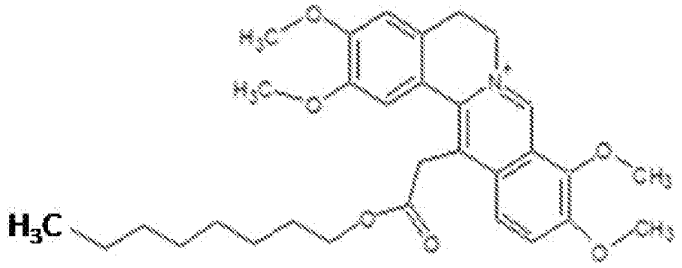
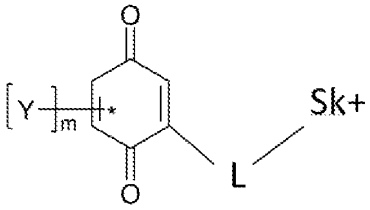
and C_nPalm (wherein n is from 4 to 12), for example C8Palm:



Also the set of compounds of Formula I includes SkQ compounds of Formula II:



Z^-

Formula II

wherein:

Y is lower alkyl or lower alkoxy,

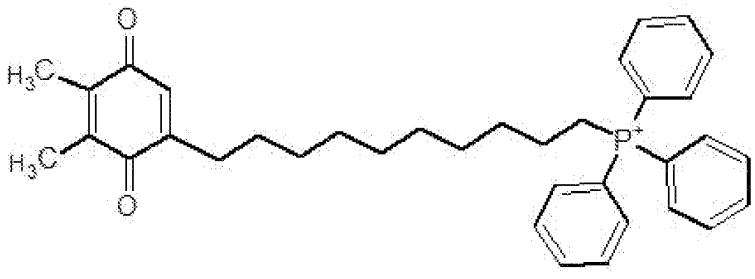
m is 0, 1, or 2

L is a linker group comprising straight or branched hydrocarbon chain of 1-40 carbon atoms, which can be optionally substituted by one or more substituents and optionally contains one or more double or triple bonds,

Sk+ is a lipophilic cation, and

Z^- is a pharmacologically acceptable anion.

An example of SkQ is the following compound, referred to herein as “SkQ1”:



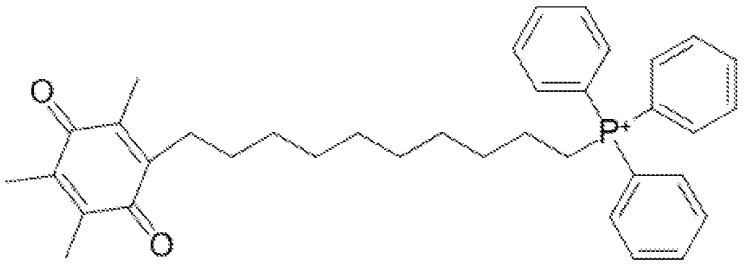
Z^-

wherein Z is pharmaceutically acceptable anion such as bromide, chloride, sulfate, mesylate etc.

As used herein, a lower alkyl or lower alkoxy can be substituted or unsubstituted and can comprise 1 to 6 carbon atoms on the alkyl or alkoxy backbone, which can be straight-chain or branched, and all endpoints are subsumed in the range from 1 to 6.

Further non-limiting examples of SkQ compounds are the following:

SkQ3



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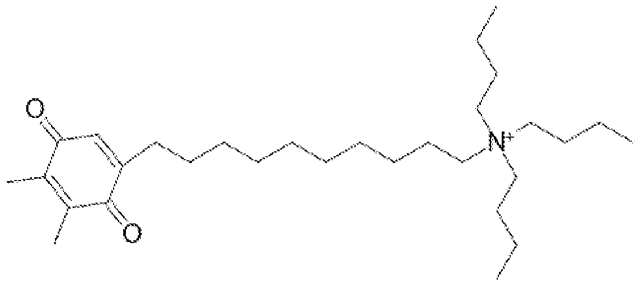
SkQ4



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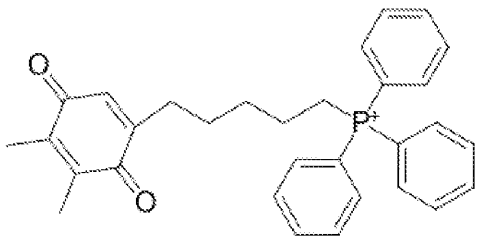
SkQ5



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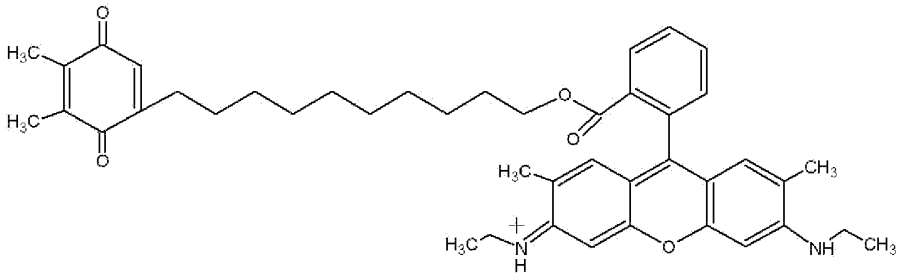
SkQR1



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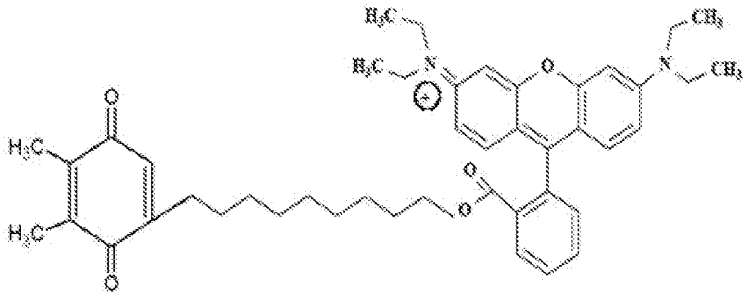
SkQRB1



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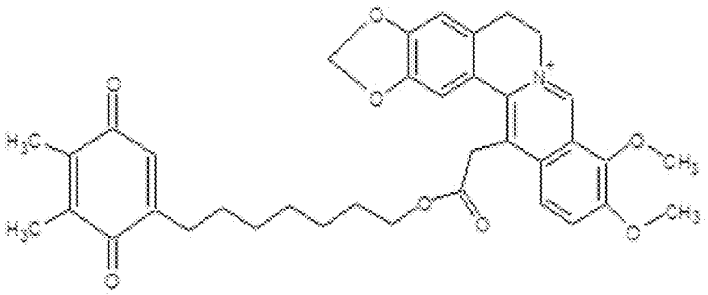
SkQB1



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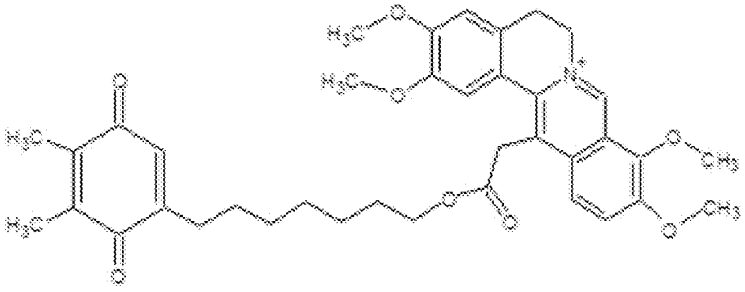
SkQBP1



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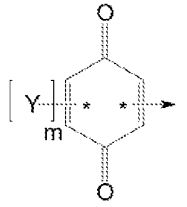
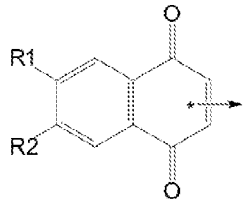
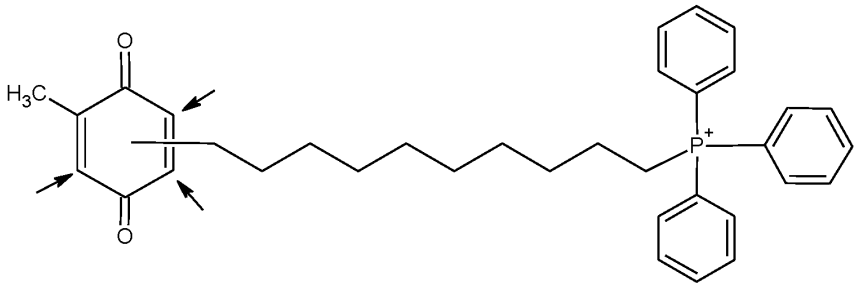
Formula II may further comprise the antioxidant below:





, or , wherein "*" indicates attachment at any ring carbon, such as to recite the example of SkQT (one isomer or a mixture of isomers that differ by the position of decyl linker, possible positions are indicated with arrows):



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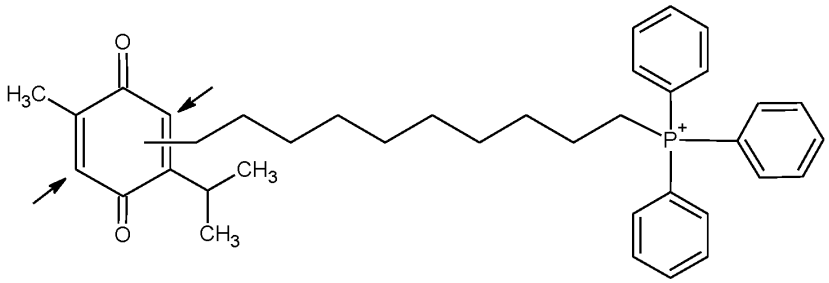
SkQThy (mixture of isomers that differ by the position of decyl linker, possible positions are indicated with arrows)



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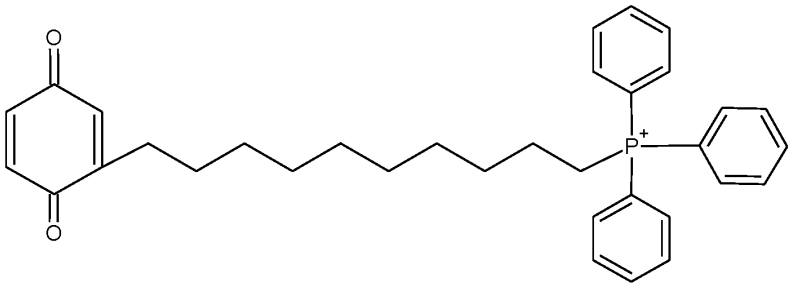
Further examples are SkQB



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In another embodiment of the invention, the mitochondrial uncoupler could be an anionic uncoupler such as DNP or BAM15, or FCCP, or CCCP, or SF 6847.

Any GLP-1 receptor antagonist can be used in the present technology. For example, the GLP-1 receptor antagonist can be liraglutide, semaglutide, tirzepatide, albiglutide, dulaglutide, exenatide, lixisenatide, or any combination thereof. The GLP-1 receptor antagonist can be administered in any form, including an extended release form. The route of administration can be by subcutaneous injection, parenteral injection, or oral administration, for example.

The technology described herein is not limited to the example compounds shown above, and any compound of the technology can be formulated in various pharmaceutical formulations as known in the art.

As used herein, the term "about" includes values close to the stated value as understood by one of ordinary skill. For example, the term "about" can refer to values within 10%, 5%, or 1%, of the stated value.

Example 1. Effects of a combination of SkQ1 and Liraglutide in Mouse Model of Diet-induced Obesity (DIO).

1. STUDY OBJECTIVE

To examine the effects of SkQ1 in combination with a GLP-1 on a DIO mouse model.

2. MATERIALS AND METHODS

2.1. Test substance

SkQ1 stock solution was diluted 10x in saline according to the study protocol. Liraglutide was prepared in phosphate buffered saline.

2.2. Induction of obesity

After exposure to the high fat diet for circa 32 weeks, 24 male mice were singly housed and placed on a reverse phase light/ dark cycle. Mice continued to be provided with high fat diet and filtered water ad libitum during the study.

2.3. Route of drug administration

SkQ1 and Liraglutide were administered subcutaneously in a volume of 5 mL/kg.

2.4. Treatment doses

SkQ1 was administered subcutaneously at a dose level of 0.5 mg/kg on days 1-21. Liraglutide was administered subcutaneously at a dose level of 0.05 mg/kg on days 1-21.

2.5. Animals

Male C57BL/6J mice were used in the study. Animals were group housed with ad libitum access to a high fat diet and filtered tap water. The mice were housed in polypropylene cages with sawdust-coated floors, red house, red tunnel, sizzle nest and nestlet at a temperature of 22±2°C. Relative humidity was typically 55±15% with prolonged periods below 40% RH or above 70% RH avoided.

2.6. Statistical tests

Daily body weight and food intake were analyzed by analysis of covariance (ANCOVA) with Day 1 body weight as a covariate.

3. EXPERIMENTAL DESIGN AND TREATMENT

3.1. Study groups

Group 1: Vehicle

Six DIO mice were subcutaneously administered vehicle [5% propylene glycol in saline] in a volume of 5 mL/kg once daily on days 1-21 of the study.

Group 2: 0.025 mg/kg Liraglutide

Six DIO mice were subcutaneously administered 0.025 mg/kg Liraglutide on days 1-21 of the study.

Group 3: 0.05 mg/kg Liraglutide

Six DIO mice were subcutaneously administered 0.05 mg/kg Liraglutide on days 1-21 of the study.

Group 4: 0.5 mg/kg SkQ1 and 0.05 mg/kg Liraglutide

Six DIO mice were subcutaneously administered 0.5 mg/kg SkQ1 and 0.05 mg/kg Liraglutide on days 1-21 of the study.

The table below summarizes the treatment schedule:

Group	No. mice	Test substance	Dose (mg/kg)	Volume (mL/kg)	Regimen
1	6	Vehicle	-	5	SC, for 21 days
2	6	Liraglutide	0.025 mg/kg	5	SC, for 21 days
3	6	Liraglutide	0.05 mg/kg	5	SC, for 21 days
4	6	Liraglutide and SkQ1 combo	0.05 mg/kg Liraglutide, 0.5 mg/kg SkQ1	5	SC, for 21 days

4. RESULTS

4.1. Weights

Animals in Groups 2-4 exhibited steady weight loss over the first 10 days of drug administration. See Fig. 1A. However, then Groups 2-3 (both standalone Liraglutide doses) quickly achieved a plateau at the same level of about 8% weight loss compared to the baseline, where the weight loss level stayed until the end of the study in those two groups. In a stark contrast, SkQ1 plus Liraglutide combo demonstrated continued weight loss efficacy until the end of the study, achieving about 13% weight loss at the end of the study. Difference in the level of weight loss in combo group vs. each individual Liraglutide group achieved statistical significance of $p<0.05$ at day 21.

4.2 Food Intake

0.025 mg/kg Liraglutide group did not show notable reduction in cumulative food intake over the 21 days of the study. See Fig. 1B. 0.05 mg/kg Liraglutide group showed a notable reduction in cumulative food intake. Combination group did not show any further reduction in cumulative food intake compared to standalone 0.05 mg/kg Liraglutide.

5. SUMMARY

Treatment with 0.5 mg/kg SkQ1 in a combo with 0.05 mg/kg Liraglutide showed a significant increase in body weight loss compared to Liraglutide alone. However, adding SkQ1 to Liraglutide treatment did not further decrease food intake, which points to a synergistic combined efficacy of the two drugs against obesity without additional impact of SkQ1 on food intake.

Example 2. Effects of a combination of SkQ1 and Liraglutide in Mouse Model of Diet-induced Obesity (DIO) with Liraglutide treatment stopped before study end.

1. STUDY OBJECTIVE

To examine the effects of SkQ1 in combination with a GLP-1 on a DIO mouse model after GLP-1 treatment is stopped.

2. MATERIALS AND METHODS

2.1. Test substance

SkQ1 stock solution was diluted 10x in saline according to the study protocol. Liraglutide was prepared in phosphate buffered saline.

2.2. Induction of obesity

After exposure to the high fat diet for circa 32 weeks, 18 male mice were singly housed and placed on a reverse phase light/ dark cycle. Mice continued to be provided with high fat diet and filtered water ad libitum during the study.

2.3. Route of drug administration

SkQ1 and Liraglutide were administered subcutaneously in a volume of 5 mL/kg.

2.4. Treatment doses

SkQ1 was administered subcutaneously at a dose level of 0.5 mg/kg on days 1-24. Liraglutide was administered subcutaneously at a dose level of 0.025 mg/kg on days 1-20 and then replaced with Vehicle injection for days 21-24.

2.5. Animals

Male C57BL/6J mice were used in the study. Animals were group housed with ad libitum access to a high fat diet and filtered tap water. The mice were housed in polypropylene cages with sawdust-coated floors, red house, red tunnel, sizzle nest and nestlet at a temperature of 22±2°C. Relative humidity was typically 55±15% with prolonged periods below 40% RH or above 70% RH avoided.

2.6. Statistical tests

Daily body weight were analyzed by a T-test.

3. EXPERIMENTAL DESIGN AND TREATMENT

3.1. Study groups

Group 1: Vehicle

Six DIO mice were subcutaneously administered vehicle [5% propylene glycol in saline] in a volume of 5 mL/kg once daily on days 1-24 of the study.

Group 2: 0.025 mg/kg Liraglutide

Six DIO mice were subcutaneously administered 0.025 mg/kg Liraglutide on days 1-20 of the study of the study only. Vehicle was injected on days 21-24.

Group 3: 0.5 mg/kg SkQ1 and 0.025 mg/kg Liraglutide

Six DIO mice were subcutaneously administered 0.5 mg/kg SkQ1 on all days 1-24 of the study. 0.025 mg/kg Liraglutide was subcutaneously administered on days 1-20 of the study only (replaced with Vehicle for days 21-24).

The table below summarizes the treatment schedule:

Group	No. mice	Test substance	Dose (mg/kg)	Volume (mL/kg)	Regimen
1	6	Vehicle	-	5	SC, for 24 days
2	6	Liraglutide	0.025 mg/kg	5	SC, for 20 first days, replaced with Vehicle for Days 21-24
3	6	Liraglutide and SkQ1 combo	0.025 mg/kg Liraglutide, 0.5 mg/kg SkQ1	5	Liraglutide: SC, for 20 first days (replaced with Vehicle for Days 21-24) SkQ1: SC, for all 24 days

4. RESULTS

4.1. Weights

Animals in Group 1 did not show any notable weight loss or gain over Days 21-24, as expected. Fig. 2A. Group 2 (Liraglutide group) demonstrated a sharp statistically significant weight gain after Liraglutide treatment was stopped on Day 21. Sharp weight gain is typical for when Liraglutide treatment had reduced weight and then is stopped. Group 3 (a combination of 0.5 mg/kg SKQ1 treatment and 0.025 Liraglutide treatment) did not exhibit any weight gain after Liraglutide treatment was stopped on Day 21, and exhibited a slight weight loss over days 21-24 attributed to continued SkQ1 treatment.

4.2 Food Intake

0.025 mg/kg Liraglutide group increased its food intake significantly after termination of Liraglutide treatment on day 21. See Fig. 2B. In the SkQ1/Liraglutide combination group such food intake increase did not occur after terminating Liraglutide treatment on day 21, which was attributed to continued SkQ1 treatment in that group.

5. SUMMARY

Termination of Liraglutide treatment often leads to a sharp weight gain in both animals and humans. We demonstrated that continued treatment with SkQ1 after Liraglutide treatment is stopped protects from such an abrupt weight gain.

Example 3. Effects of a combination of SkQ1 and Liraglutide in Mouse Model of Diet-induced Obesity (DIO) with both Liraglutide and SKQ1 treatments stopped before study end.

1. STUDY OBJECTIVE

To examine the effects of SkQ1 in combination with a GLP-1 on a DIO mouse model after SkQ1 and GLP-1 treatments are stopped.

2. MATERIALS AND METHODS

2.1. Test substance

SkQ1 stock solution was diluted 10x in saline according to the study protocol. Liraglutide was prepared in phosphate buffered saline.

2.2. Induction of obesity

After exposure to the high fat diet for circa 32 weeks, 18 male mice were singly housed and placed on a reverse phase light/ dark cycle. Mice continued to be provided with high fat diet and filtered water ad libitum during the study.

2.3. Route of drug administration

SkQ1 and Liraglutide were administered subcutaneously in a volume of 5 mL/kg.

2.4. Treatment doses

SkQ1 was administered subcutaneously at a dose level of 0.025 mg/kg on days 1-14, which then was increased to 1 mg/kg for days 15-20 and then replaced with Vehicle injection for days 21-24. Liraglutide was administered subcutaneously at a dose level of 0.025 mg/kg on days 1-20 and then replaced with Vehicle injection for days 21-24.

2.5. Animals

Male C57BL/6J mice were used in the study. Animals were group housed with ad libitum access to a high fat diet and filtered tap water. The mice were housed in polypropylene cages with sawdust-coated floors, red house, red tunnel, sizzle nest and nestlet at a temperature of 22±2°C. Relative humidity was typically 55±15% with prolonged periods below 40% RH or above 70% RH avoided.

2.6. Statistical tests

Daily body weight were analyzed by a T-test.

3. EXPERIMENTAL DESIGN AND TREATMENT

3.1. Study groups

Group 1: Vehicle

Six DIO mice were subcutaneously administered vehicle [5% propylene glycol in saline] in a volume of 5 mL/kg once daily on days 1-24 of the study.

Group 2: 0.025 mg/kg Liraglutide

Six DIO mice were subcutaneously administered 0.025 mg/kg Liraglutide on days 1-20 of the study of the study only. Vehicle was injected on days 21-24.

Group 3: 0.25/1.0 mg/kg SkQ1 and 0.025 mg/kg Liraglutide

Six DIO mice were subcutaneously administered 0.25 mg/kg SkQ1 on all days 1-14 of the study, which then was increased to 1 mg/kg for days 15-20 and replaced with Vehicle for days 21-24. 0.025 mg/kg Liraglutide was subcutaneously administered on days 1-20 of the study only (replaced with Vehicle for days 21-24).

The table below summarizes the treatment schedule:

Group	No. mice	Test substance	Dose (mg/kg)	Volume (mL/kg)	Regimen
1	6	Vehicle	-	5	SC, for 24 days
2	6	Liraglutide	0.025 mg/kg	5	SC, for 20 first days, replaced with Vehicle for Days 21-24
3	6	Liraglutide and SkQ1 combo	0.025 mg/kg Liraglutide, 0.25/1.0 mg/kg SkQ1	5	Liraglutide: SC, for 20 first days (replaced with Vehicle for Days 21-24) SkQ1: 0.25 mg/kg SC, for first 14 days, increased to 1.0 mg/kg for days 15-20 and replaced with Vehicle for days 21-24

4. RESULTS

4.1. Weights

Animals in Group 1 did not show any notable weight loss or gain over Days 21-24, as expected. See Fig. 3A. Group 2 (Liraglutide group) demonstrated a sharp statistically significant weight gain after Liraglutide treatment was stopped on Day 21. Sharp weight gain is typical for when Liraglutide treatment had reduced weight and then is stopped. Group 3 (a combination of 0.25/1.0 mg/kg SKQ1 treatment and 0.025 Liraglutide treatment) exhibited a milder increase in weight after all treatments were stopped on Day 21, showing significantly lower weight gain than Liraglutide group on day 23.

4.2 Food Intake

0.025 mg/kg Liraglutide group increased its food intake significantly after termination of Liraglutide treatment on day 21. See Fig. 3B. In the SkQ1/Liraglutide combination group such food intake increase also occurred after treatments were stopped, but at lower numerical values and lower statistical significance, which was attributed to SkQ1 treatment in that group prior to treatment termination.

5. SUMMARY

Termination of Liraglutide treatment often leads to a sharp weight gain in both animals and humans. We demonstrated that treatment with SkQ1 prior to terminating both treatments protects from such an abrupt weight gain.

Example 4. Effects of two different doses of SkQ1 in Mouse Model of DIO.

1. STUDY OBJECTIVE

To examine the effects of two doses of SkQ1 on a DIO mouse model.

2. MATERIALS AND METHODS

2.1. Test substance

SkQ1 stock solution was diluted 10x in saline according to the study protocol.

2.2. Induction of obesity

After exposure to the high fat diet for circa 32 weeks, 24 male mice were singly housed and placed on a reverse phase light/ dark cycle. Mice continued to be provided with high fat diet and filtered water ad libitum during the study.

2.3. Route of drug administration

SkQ1 was administered subcutaneously in a volume of 5 mL/kg.

2.4. Treatment doses

SkQ1 was administered subcutaneously at two dose levels of 0.05 mg/kg and 1.0 mg/kg on days 1-14.

2.5. Animals

Male C57BL/6J mice were used in the study. Animals were group housed with ad libitum access to a high fat diet and filtered tap water. The mice were housed in polypropylene cages with sawdust-coated floors, red house, red tunnel, sizzle nest and nestlet at a temperature of 22±2°C. Relative humidity was typically 55±15% with prolonged periods below 40% RH or above 70% RH avoided.

2.6. Statistical tests

Daily body weight were analyzed by a T-test.

3. EXPERIMENTAL DESIGN AND TREATMENT

3.1. Study groups

Group 1: Vehicle

Eight DIO mice were subcutaneously administered vehicle [5% propylene glycol in saline] in a volume of 5 mL/kg once daily on days 1-14 of the study.

Group 2: 0.5 mg/kg SkQ1

Eight DIO mice were subcutaneously administered 1.0 mg/kg SkQ1 on days 1-14.

Group 3: 1.0 mg/kg SkQ1

Eight DIO mice were subcutaneously administered 1.0 mg/kg SkQ1 on days 1-14.

The table below summarizes the treatment schedule:

Group	No. mice	Test substance	Dose (mg/kg)	Volume (mL/kg)	Regimen
1	8	Vehicle	-	5	SC, for 14 days
2	8	SkQ1	0.5 mg/kg	5	SC, for 14 days
3	8	SkQ1	1.0 mg/kg	5	SC, for 14 days

4. RESULTS

4.1. Weights

Animals in Group 1 showed insignificant low-level weight loss over Days 1-14. See Fig. 4A. Group 2 (0.5 mg/kg SkQ1) demonstrated a statistically significant weight decline over the course of the study. Group 3 (1.0 mg/kg SkQ1) demonstrated a steeper and more significant weight loss over the course of the study.

4.2 Food Intake

0.5 mg/kg SkQ1 treatment demonstrated a statistically significant decrease in cumulative food intake during the study compared to Vehicle. See Fig. 4B. 1.0 mg/kg SkQ1 treatment demonstrated a higher reduction in food intake, which was also more significant.

5. SUMMARY

SkQ1 treatments demonstrated dose-dependent reduction in weight and food intake during 14 days of the study. Weight loss curves highlighted a steady, linear weight loss trend over the two weeks of treatment.

CLAIMS

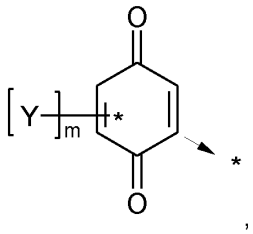
1. A method to aid in treating or preventing obesity and/or an obesity-associated disease or medical condition, the method comprising the step of administering to a subject in need thereof therapeutically or prophylactically effective amounts of a mitochondrial uncoupler and a glucagon-like peptide-1 receptor agonist.

2. The method of claim 1, wherein the mitochondrial uncoupler is an SkQ compound of Formula I below:



Formula I

wherein A is hydrogen or an effector moiety, which is an antioxidant optionally having a following structure:



,

and/or reduced forms thereof,

wherein m is from 0 to 3; each Y is independently selected from the group consisting of: lower alkyl (1 to 6 carbons), lower alkoxy (1 to 6 carbons);

L is a linker group, comprising:

a) straight or branched hydrocarbon chain which can be optionally substituted by one or more substituents and optionally contains one or more double or triple bonds;

b) a natural isoprene chain;

n is the number of carbon atoms in the linker, which is an integer from 1 to 40; and

B is a mitochondria targeting group comprising a lipophilic cation;

and a pharmacologically acceptable anion;

and/or solvates, salts, isomers, or prodrugs thereof.

3. The method of claim 1 or claim 2, wherein the mitochondrial uncoupler is selected from the group consisting of SkQ1, SkQ3, SkQ4, SkQ5, SkQR1, SkQBR1, SkQB1, SkQBP1, MitoQ, C12TPP, C10TPP, C10R1, C4R1, C8Berb, and C8Palm.

4. The method of any of the preceding claims, wherein the GLP-1 receptor agonist is selected from the group consisting of liraglutide, semaglutide, tirzepatide, albiglutide, dulaglutide, exenatide, lixisenatide, and combinations thereof.

5. The method of any of the preceding claims, wherein the obesity associated disease or medical condition is selected from the group consisting of non-alcoholic fatty liver disease, non-alcoholic steatohepatitis (NASH), and metabolic dysfunction-associated steatohepatitis (MASH).

6. The method of any of the preceding claims, wherein said mitochondrial uncoupler and glucagon-like peptide-1 receptor agonist are both administered to the subject for a period of days.

7. The method of any of the preceding claims, wherein the period of days continues for at least 7, at least 10, at least 14, at least 20, at least 21, at least 28, or at least 30 days.

8. The method of any of the preceding claims, wherein administering said mitochondrial uncoupler continues after administering the glucagon-like peptide-1 receptor agonist is paused or terminated.

9. The method of claim 8, wherein administering said mitochondrial uncoupler continues after administering the glucagon-like peptide-1 receptor agonist is paused or terminated for at least 3, at least 5, at least 7, at least 10, at least 14, at least 20, at least 21, at least 28, or at least 30 days.

10. The method of claim 8 or claim 9, wherein weight regain after administering the glucagon-like peptide-1 receptor agonist is paused or terminated is substantially prevented by said continued administering of said mitochondrial uncoupler.

11. The method of any of the preceding claims, wherein said glucagon-like peptide-1 receptor agonist is administered by subcutaneous injection, and wherein said mitochondrial uncoupler is administered by subcutaneous injection or by another route of administration.

12. A pharmaceutical composition for use in performing the method of any of the preceding claims.

13. The pharmaceutical composition for use of claim 12, wherein the composition comprises a GLP-1 receptor agonist, a mitochondrial uncoupler, and one or more excipients.

14. A pharmaceutical kit comprising a first pharmaceutical composition comprising a GLP-1 receptor agonist and a second pharmaceutical composition comprising a mitochondrial uncoupler.

15. The pharmaceutical kit of claim 14, wherein said first and second pharmaceutical compositions are separately packaged and/or present as separate dosage forms and/or formulations.