



(51) International Patent Classification:

A61K 31/198 (2006.01) *A61P 3/10* (2006.01)
A61K 31/155 (2006.01)

(21) International Application Number:

PCT/CN2014/075963

(22) International Filing Date:

22 April 2014 (22.04.2014)

(25) Filing Language:

English

(26) Publication Language:

English

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) Title: ORNITHINE-CONTAINING OR ASPARTATE-CONTAINING COMPOSITIONS AND THE USES THEREOF

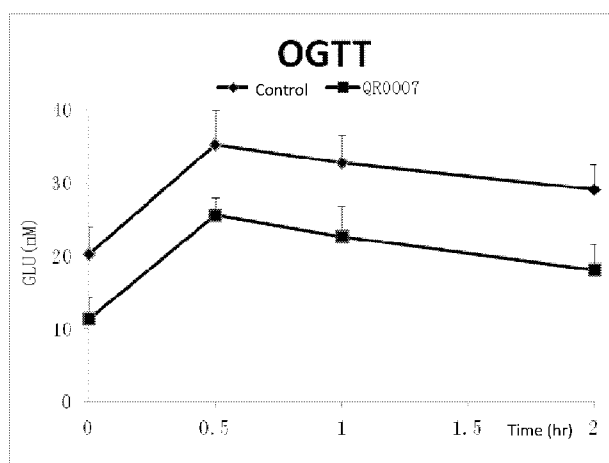


Figure 1

(57) Abstract: Methods and compositions comprising ornithine and/or aspartate that are useful for lowering serum glucose level, treating diabetes or hyperglycemia are described. Methods of using compositions comprising ornithine and/or aspartate for ameliorating the side-effect induced by a therapeutic agent (e.g., anti-hyperglycemic agents) are also described.

ORNITHINE- CONTAINING OR ASPARTATE-CONTAINING COMPOSITIONS AND THE USES THEREOF

BACKGROUND OF THE INVENTION

[0001] Diabetes mellitus (DM) or diabetes, is a group of metabolic diseases characterized by an excessive level of glucose in the bloodstream, also known as hyperglycemia. Diabetes is one of the major diseases that endangers the public health due to its prevalence, morbidity and mortality. In recent years, the onset of diabetes or associated conditions has appeared in younger patients. Clinical symptoms of diabetes can be polyphagia, polydipsia, polyuria, fatigue, weight loss, blurred vision, poor wound healing, dry mouth, dry or itchy skin, tingling in feet or heels, erectile dysfunction, recurrent infections, external ear infections, cardiac arrhythmia, stupor, coma or seizures. Diabetes can further lead to hypertension, hyperlipidemia, coronary heart disease, chronic renal failure and other complications.

[0002] Diabetes can be categorized into two types: type I diabetes and type II diabetes. Type I diabetes is caused by the functional decline of the pancreatic β –cells. Type I diabetes patients are prone to acute complications, such as ketoacidosis. Type II diabetes is a complex metabolic disorder with different level of pathological symptoms. It can be characterized by the decline of islet β –cell functions, insulin resistance and glycogen metabolism disorders.

[0003] In clinic, hyperglycemia or diabetes can be treated by various medications or anti-hyperglycemic agents, such as biguanides, sulfonylureas, thiazolidinediones, glinides, DPP-IV inhibitor, insulin and insulin analogues or statins. Although many of the anti-hyperglycemic agents can lower the serum glucose level in a patient, most patients still require the use of more effective anti-hyperglycemic agents every 3 to 4 years to maintain sufficient blood sugar level management. Common side effects associated with the anti-hyperglycemic agents such as hypoglycemia, weight gain, gastrointestinal adverse reactions, edema, or increase in cardiovascular events in diabetic patients, have hindered its long-term clinical applicability and success. While some statin medications are generally effective and safe for treatment of hyperglycemia, there has been clinical evidence indicating that chronic administration of statins, can result in rhabdomyolysis and myopathy. These adverse effects are dose related, and can induce serious muscle pain and weakness. Furthermore, various side-effects such as constipation, rhinitis, pharyngitis, sore throat, urinary tract infection, joint pain, high blood pressure, dizziness and other symptoms have been reported for statin medications.

[0004] Ornithine and aspartate can complex together in a salt form, as referred to “ornithine-aspartate” herein. The symbol “-” that is placed in between two entities refers to an ionic bonding in between, wherein one entity is a counter ion of the other entity. Ornithine-aspartate is primarily used to treat conditions such as hepatic encephalopathy, hepatitis, hepatic steatosis, jaundice, liver cirrhosis in clinic. In cirrhosis, impaired hepatic metabolism and blood flow lead to raised serum and CNS ammonia concentrations. Ornithine and aspartate are amino acids which are important in the biochemical pathways that detoxify ammonia. Abnormal ammonia metabolism and the resulting accumulation of toxic ammonia is one of several possible mechanisms for hepatic encephalopathy. Ornithine and aspartate are substrates in metabolizing ammonia to urea and glutamine, respectively. L-Ornithine is one of the products of the action of the enzyme arginase on L-arginine, creating urea. L-ornithine supplementation may attenuate fatigue in subjects, in increasing the efficiency of energy consumption and promoting the excretion of ammonia (Sugino et al. (2008) "L-ornithine supplementation attenuates physical fatigue in healthy volunteers by modulating lipid and amino acid metabolism", Nutrition Research 28(11):738-43). L-Ornithine may also reduce mental stress of a subject (Kurata et al. (2011) "Orally administered L-ornithine elevates brain L-ornithine levels and has an anxiolytic-like effect in mice", Nutritional Neuroscience 14(6):243-8).

SUMMARY OF THE INVENTION

[0005] As noted above, there exists a pressing need for compositions and methods that can effectively reduce serum glucose level, treating hyperglycemia and diabetes in a subject. Similarly, there is also a need for reducing side-effects of many anti-hyperglycemic agents. The present invention addresses these needs and provides related advantages as well.

[0006] In one embodiment, the present invention provides a method of lowering serum glucose level in a subject with hyperglycemia. The method comprises identifying a subject suffering from hyperglycemia, wherein the subject has a serum glucose level of higher than about 100 mg/dL after fasting for about 8 to 12 hours; administering to said subject a composition comprising ornithine and/or aspartate (including but not limited to ornithine-aspartate (OA)) in an amount that is effective in lowering the serum glucose level.

[0007] In practicing any of the methods provided herein, the composition administered to a subject can contain at least a portion of ornithine (O) and aspartate (A) that is complexed in a salt form of ornithine-aspartate (OA). In another aspect, the composition administered to a subject can contain ornithine and a

counter anion disclosed herein. In yet another aspect, the composition administered to a subject can contain aspartate and a counter cation disclosed herein. Where desired alternatively, the composition administered comprises free form of ornithine and/or free form of aspartate. In some aspects, the composition administered comprises ornithine and/or aspartate in its pharmaceutically accepted salt forms.

[0008] In one aspect, the amount of ornithine and/or aspartate (including but not limited to ornithine-aspartate (OA)) administered is about 0.01 g to 20 g daily. In another aspect, the amount of ornithine and/or aspartate administered is at least 0.5, 1 or 3 g daily. In yet another aspect, the amount of ornithine and/or aspartate administered is at least 3 g daily.

[0009] In some aspects, the subject disclosed herein suffers from diabetes. In some aspect, the methods as described herein further comprises administering an amount of an anti-hyperglycemic agent to said subject. The anti-hyperglycemic agent can be selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, glinides, DPP-IV inhibitor, insulin and insulin analogues. The anti-hyperglycemic agent can be Metformin or Sitagliptin. The amount of the anti-hyperglycemic agent administered can be a sub-therapeutic amount.

[0010] The methods disclosed herein may involve administration of the composition disclosed via oral ingestion, intravenous administration, inhalation, nasal insufflation, intra-arterial injection, subcutaneous administration, mucosal administration, or pharyngeal administration. The composition as described herein can be administered orally. Administration of the subject composition can take place for at least about 2 weeks, or at least about 1 months or longer. The subject composition can be administered for at least about 1, 2, 3, 4, 5, 6 months or longer. The composition administered can be contained in a foodstuff or in a pharmaceutical composition.

[0011] In some embodiments, the methods disclosed herein can be used to decrease the fasting serum glucose level of the subject. In some embodiments, the methods described herein can decrease the serum glucose level in the subject after a glucose tolerance test. The subject being identified in the methods as disclosed herein can exhibit a serum glucose level of higher than about 125 mg/dL after fasting for about 8 to 12 hours prior to said administering.

[0012] In another aspect, a method of administering an anti-hyperglycemic agent to a subject in need thereof is disclosed. The method can comprise administering an amount of the anti-hyperglycemic agent in conjunction with an effective amount of a composition comprising ornithine and/or aspartate, wherein the anti-hyperglycemic agent and the composition comprising ornithine and/or aspartate synergistically lower the serum glucose level in said subject.

[0013] In practicing any of the methods provided herein, the subject composition can be administered orally. In some cases, the subject composition can be administered prior to, subsequent to, or concurrent with administering the anti-hyperglycemic agent.

[0014] In another aspect, the subject composition can be administered daily. The amount of ornithine and/or aspartate administered can be about 0.01 g to 20 g daily. In some cases, the amount of ornithine and/or aspartate administered is at least 3 g daily.

[0015] In yet another aspect, the amount of the anti-hyperglycemic agent can be a sub-therapeutic amount. A side-effect of the anti-hyperglycemic agent can be reduced. Where desired alternatively, the anti-hyperglycemic agent is selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, meglitinides, glinides, α -glucosidase inhibitors, repaglinide, nateglinide, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin or insulin and insulin analogues, and any combination thereof. In some embodiments, the anti-hyperglycemic agent is Metformin or Sitagliptin.

[0016] In practicing any of the methods as disclosed herein, the subject composition and the anti-hyperglycemic agent can be administered as a single unit dose. In some cases, the unit dosage is in a form of a tablet, a capsule, a pill, a granule, an emulsion, a gel, a plurality of beads encapsulated in a capsule, a powder, a suspension, a liquid, a semi-liquid, a semi-solid, a syrup, a slurry or a chewable.

[0017] The present invention also provides a method of lowering a side-effect of an anti-hyperglycemic agent in a subject in need thereof, comprising administering to the subject an effective amount of a composition comprising ornithine and/or aspartate in conjunction with a sub-therapeutic amount of an anti-hyperglycemic agent, thereby reducing a side-effect of the anti-hyperglycemic agent in said subject. In some cases, the composition is administered orally. The composition can be administered daily. In some cases, the amount of ornithine and/or aspartate administered is about 0.01 g to 20 g daily. In another case, the amount of ornithine and/or aspartate administered is at least 3 g daily.

[0018] In one aspect, the anti-hyperglycemic agent administered can be selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, meglitinides, glinides, α -glucosidase inhibitors, repaglinide, nateglinide, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin or insulin and insulin analogues, and any combination thereof. In another aspect, the anti-hyperglycemic agent is Metformin or Sitagliptin.

[0019] When practicing the methods as described herein, the composition comprising ornithine and/or aspartate can be in an amount effective in lowering serum glucose level in said subject administered. In some embodiments, the composition comprising ornithine and/or aspartate and the anti-hyperglycemic agent synergistically lower the serum glucose level in said subject administered.

[0020] The present invention also provides a composition comprising: (a) a sub-therapeutic amount of an anti- hyperglycemic agent; and (b) an effective amount of ornithine and/or aspartate, wherein the composition is capable of synergistically lower the serum glucose level in a subject administered said composition as compared to administering to the subject component (a) or component (b) alone. In one aspect, the subject composition is formulated in a unit dosage form. In another aspect, the composition is formulated in a solid or liquid form. In yet another aspect, the solid or liquid dosage form is a tablet, a capsule, a pill, a granule, an emulsion, a gel, a plurality of beads encapsulated in a capsule, a powder, a suspension, a liquid, a semi-liquid, a semi-solid, a syrup, a slurry or a chewable form. In still yet another aspect, the composition is formulated for oral consumption, intravenous injection, inhalation, nasal insufflation, intraarterial injection, subcutaneous administration, mucosal administration, or pharyngeal administration. The subject composition can be formulated for oral consumption.

[0021] In some aspects, the component (a) and component (b) in the subject composition are separately packaged. In another aspect, component (a) and component (b) can be mixed. In another aspect, the anti- hyperglycemic agent can be selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, meglitinides glinides, α -glucosidase inhibitors, repaglinide, nateglinide, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin or insulin and insulin analogues, and any combination thereof. In another aspect, the anti- hyperglycemic agent is Metformin or Sitagliptin.

[0022] In another aspect, the subject composition comprising ornithine and/or aspartate can be present in an amount effective in lowering serum glucose level in a subject in need thereof. In yet another aspect, the composition comprises about 0.01 to 20 g of ornithine and/or aspartate (including but not limited to ornithine-aspartate (OA)). In still yet another aspect, the composition comprises at least about 1 g of ornithine and/or aspartate (including but not limited to ornithine-aspartate (OA)). In still yet another aspect, the composition comprises at least about 3 g of ornithine and/or aspartate (including but not limited to ornithine-aspartate (OA)).

[0023] In some cases, the subject composition can be formulated for a daily dosage form. The composition can be capable in lowering a side effect of the anti-hyperglycemic agent as compared to administering to the subject a therapeutic amount of the anti-hyperglycemic agent alone.

INCORPORATION BY REFERENCE

[0024] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0026] **Figure 1:** Effects of QR0007 (ornithine-aspartate composition) on the oral glucose tolerance test of the hyperlipidemic and hyperglycemic rats (mean $\pm$ sem, n=7).

[0027] **Figure 2:** Effects of ornithine-aspartate (QR0007) in different dosages on the serum glucose level in the hyperlipidemic and hyperglycemic rats (mean $\pm$ sem, n=6-8).

[0028] **Figure 3:** Effects of ornithine-aspartate (QR0007) and combination treatment with anti-hyperglycemic agents on the serum glucose level of BKS-DM mice ((mean $\pm$ sem, n=6).

DETAILED DESCRIPTION OF THE INVENTION

[0029] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms “a”, “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms “including”, “includes”, “having”, “has”, “with”, or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term “comprising”.

[0030] The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to 20%, up to 10%, up to 5%, or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular

values are described in the application and claims, unless otherwise stated the term “about” meaning within an acceptable error range for the particular value should be assumed.

[0031] “Treatment”, “treating”, “palliating” and “ameliorating”, as used herein, are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0032] As used herein, “agent” refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include simple or complex organic or inorganic molecule, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, antibody fragment, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound. Various compounds can be synthesized, for example, small molecules and oligomers (e.g., oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of the present invention.

[0033] Generally, the term “concurrent administration”, “co-administration”, or “administration in conjunction with” in reference to two or more subjects of administration for administration to a subject body, such as components, agents, substances, materials, compositions, and/or the like, refers to administration performed using dose(s) and time interval(s) such that the subjects of administration are present together within the subject body, or at a site of action in the subject body, over a time interval in less than de minimus quantities. The time interval may be any suitable time interval, such as an appropriate interval of minutes, hours, days, or weeks, for example. The subjects of administration may be administered together, such as parts of a single composition, for example, or otherwise. The subjects of administration may be administered substantially simultaneously (such as within less than or equal to about 5 minutes, about 3 minutes, or about 1 minute, of one another, for example) or within a short time of one another (such as within less than or equal to about 1 hour, 30 minutes, or 10 minutes, or within more than about 5 minutes up to about 1 hour, of one another, for example). The subjects of

administration so administered may be considered to have been administered at substantially the same time. One of ordinary skill in the art will be able to determine appropriate dose(s) and time interval(s) for administration of subjects of administration to a subject body so that same will be present at more than de minimus levels within the subject body and/or at effective concentrations within the subject body. When the subjects of administration are concurrently administered to a subject body, any such subject of administration may be in an effective amount that is less than an effective amount that might be used were it administered alone.

[0034] The term "effective amount," or "therapeutic amount" which is further described herein, encompasses both this lesser effective amount and the usual effective amount, and indeed, any amount that is effective to elicit a particular condition, effect, and/or response. As such, a dose of any such subject of concurrent administration may be less than that which might be used were it administered alone. One or more effect (s) of any such subject (s) of administration may be additive or synergistic. Any such subject(s) of administration may be administered more than one time. The effective amount may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of proliferation or down-regulation of activity of a target protein. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0035] A "sub-therapeutic amount" of an agent or therapy is an amount less than the effective amount for that agent or therapy, an amount below which would be considered therapeutic. However when such amount is combined with an effective or a sub-therapeutic amount of another agent or therapy, it can produce a result desired by the physician, due to, for example, synergy in the resulting efficacious effects, or reduction of side effects of one or more of the agents used in the combination. For example, FDA guidelines can suggest a specified level of dosing to treat a particular condition, and a sub-therapeutic amount would be any level that is below the FDA suggested dosing level.

[0036] A "synergistically effective therapeutic amount" of an agent or therapy is an amount which, when combined with an effective or sub-therapeutic amount of another agent or therapy, produces a greater effect than when either of the two agents or therapies are used alone. In some embodiments, a

synergistically effective therapeutic amount of an agent or therapy produces a greater effect when used in combination than the additive effects of each of the two agents or therapies when used alone.

[0037] A “therapeutic effect,” as used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0038] The term “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0039] “Pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated.

Supplementary active ingredients can also be incorporated into the compositions.

[0040] “Subject” refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics, pre-clinical, and veterinary applications. In some embodiments, the subject is a mammal, and in some embodiments, the subject is human.

[0041] The term “*in vivo*” refers to an event that takes place in a subject’s body.

[0042] As previously mentioned, anti-hyperglycemic agents or other anti-diabetes treatment that are known in the art may not be capable of effectively and safely reducing serum levels of glucose or treating diabetes for long term. The “serum” level refers to a physiological level, and in some embodiments, “serum level” may refer to the level in body fluid including plasma level or bloodstream level. Therefore, there exists a clinical mandate for compositions and methods that are useful for effectively and safely reducing serum levels of glucose for treatment of hyperglycemia or diabetes. In addition, there is a need for reducing the side-effects of the anti-hyperglycemic agents such as statins. The present invention provides compositions comprising amino acids ornithine and/or aspartate and methods that can address the needs. The subject compositions and methods may be useful for lowering glucose level in bloodstream or serum. In some cases, a sub-therapeutic amount of a anti-hyperglycemic agent that is known in the medical art can be administered in conjunction with the subject compositions. The subject compositions and methods may also be useful in reducing side effects of the anti-hyperglycemic agent (e.g., statin). A description of various aspects, features, embodiments, and examples, is provided herein.

[0043] Disclosed herein are compositions comprising ornithine and/or aspartate, and the methods of using the compositions. Compositions comprising ornithine and/or aspartate may be effective in lowering the glucose levels in serum of the subject. The glucose levels that can be lowered by the subject compositions can be a fasting glucose level, a glucose level after a meal, or during a glucose tolerance test. The compositions comprising ornithine and/or aspartate can be administered alone or in combination with an anti-hyperglycemic agent. In some embodiments, compositions comprising ornithine and/or aspartate may be effective to reducing a side-effect of an anti-hyperglycemic agent. In some embodiments, compositions comprising ornithine and/or aspartate may be effective to treat hyperglycemia or a condition that is associated hyperglycemia such as diabetes. The methods and compositions may comprise ornithine but not aspartate. The methods and compositions may comprise aspartate but not ornithine. The methods and compositions may comprise both ornithine and aspartate that are not complexed together.

[0044] The subject compositions may comprise ornithine. The ornithine may be complexed with a counter cation. The counter cation may be any cation that is known in the art. Non-limiting examples of counter cation include aspartate, glutamate, chloride, sulfate, phosphate, carbonate, acetate, lactate, and citrate. Aspartate is non-essential in mammals, being produced from oxaloacetate by transamination. It can also be generated from ornithine and citrulline in the urea cycle. Aspartic acid may be used to prevent fatigue or hepatic disturbance. Aspartate is known to be the carboxylate anion, salt, or ester of

aspartic acid. The subject compositions may comprise aspartate. The aspartate may be complexed with a counter anion. The counter anion may be any anion that is known in the art. Non-limiting examples of the counter anion may include, arginine, cysteine, glutamine, glycine, serine, sodium, calcium, magnesium, and potassium. The ornithine-counter cation and/or aspartate-counter-anion may be in salt form.

[0045] Such a composition, such as that appropriate for administration to a subject, may comprise at least one ornithine-comprising component and/or aspartate-comprising component. The ornithine- and/or aspartate-comprising components may be any suitable ornithine- and/or aspartate--comprising component, such as a suitably bioavailable ornithine- and/or aspartate-comprising component. The ornithine- and/or aspartate-comprising component may be any suitable biologically acceptable ornithine- and/or aspartate-comprising component. The ornithine- and/or aspartate-comprising component may be any suitable organic acid salt. Merely by way of example, the ornithine- and/or aspartate-comprising component may be a ornithine and/or aspartate salt of an amino acid.

[0046] In one embodiment, the composition of the invention may comprise at least one ornithine- and/or aspartate-counter ion compound. In other embodiments, the invention includes compositions comprising 2, 3, 4, 5, or more ornithine- and/or aspartate-counter ion compounds. In other embodiments, the counter ion(s) will be organic. In some embodiments, the organic counter ion will have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more carbon atoms.

[0047] The methods and compositions described herein may comprise ornithine and aspartate that are complexed with each other to form ornithine-aspartate in a salt form. The “-” refers to an ionic bond in between the two entities that are complexed together to form a salt. The ornithine and aspartate may be complexed using methods that are known in the art (Marumo, US 3,360,549). The Ornithine-aspartate (OA) in a salt form has been used in the treatment of cirrhosis that is well known in the art (Sikorska et al. (2010) *"Physiological functions of L-ornithine and L-aspartate in the body and the efficacy of administration of L-ornithine-L-aspartate in conditions of relative deficiency"*, Polski Merkuriusz Lekarski 28(168):490-5). A preparation of L-ornithine and L-aspartate complex may used to increase the generation of urea through the urea cycle, a metabolic pathway that removes ammonia by turning it into the neutral substance urea. It may be combined with lactulose and/or rifaximin if these alone are ineffective at controlling symptoms. As described in the current invention, methods and compositions comprising ornithine-aspartate may be used to lower the serum level of glucose, or to reduce a side-effect of a therapeutic agent (e.g., anti-hyperglycemic agent, statin). A “therapeutic agent” refers to an agent that is effective in ameliorating diabetes or hyperglycemia when administered to a subject

suffering diabetes or hyperglycemia in an effective amount. A therapeutic agent for treatment of diabetes can be an anti-diabetes agent or an anti-hyperglycemic agent.

[0048] A composition appropriate for administration to a subject with hyperglycemia or a condition that is association with hyperglycemia such as diabetes may comprise ornithine and/or aspartate. In some embodiments, a portion of the composition may comprise ornithine-aspartate as a complex. The ornithine-aspartate may be complexed with each other in a 1:1 ratio. In some embodiments, the composition may comprise ornithine in complex with a counter anion. The composition may comprise aspartate in complex with a counter cation. In some cases, the composition may comprise both the ornithine-counter anion and the aspartate-counter cation in a ratio. For example, the ratio may be 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1:4.5, 1:5, 1:5.5, 1:6, 1:6.5, 1:7, 1:7.5, 1:8, 1:8.5, 1:9, 1:9.5, 1:10, 1:10.5, 1:11, 1:11.5, 1:12, 1:12.5, 1:13, 1:13.5, 1:14, 1:14.5, 1:15, 1:15.5, 1:16, 1:16.5, 1:17, 1:17.5, 1:18, 1:18.5, 1:19, 1:19.5 or 1:20. The composition may comprise ornithine and/or aspartate in combinations with any other types of amino acid. The composition may further comprise at least one type of amino acid other than ornithine and/or aspartate. The amino acid may be a non-essential amino acid or an essential amino acid. The amino acid may be a natural amino acid or a non-natural amino acid. The amino acid may be in its salt form. The composition may comprise ornithine and/or aspartate in a salt form. The composition may comprise ornithine and/or aspartate in a dissociated ionic form. The amino acid may be Leucine, Isoleucine, Histadine, Valine, Lysine, Methionine, Phenylalanine, Threonine, Tryptophan, Arginine, Cysteine, Tyrosine, Alanine, Aspartic Acid, Glutamic Acid, Cystine, Glutamine, Glycine, Ornithine, Serine, Proline, or Taurine. The amino acid, except for glycine, may be in a L form or D form, wherein the L and D forms of an amino acid are enantiomers. The ornithine may be L-ornithine. The aspartate may be L-aspartate.

[0049] Such a composition may be prophylactically and/or therapeutically suitable or beneficial. The subject composition may be suitable for relatively rapid ornithine and/or aspartate intake, provision, and/or supplementation, as may be suitable or beneficial for any of a variety of applications, such as a nutritional or prophylactic application, and/or a therapeutic application. The composition may be a suitable or beneficial vehicle for ornithine and/or aspartate intake, provision, and/or supplementation application(s), such as any that may be accomplished via a dietary vehicle or a consumable vehicle, such as a foodstuff and/or a beverage, for example.

[0050] In some embodiments, the composition comprising ornithine and/or aspartate may be in a single dosage form. In some cases, the composition can be in multiple dosage forms. The compositions can be administered in a single dose or multiple doses. Dosing may be about once, twice, three times, four

times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In preferred embodiments, dosing may be at least once daily. In another embodiment, ornithine and/or aspartate and/or one or more therapeutic agents (e.g., anti-hyperglycemic agents or anti-diabetes agents) may be administered together about once per day to about 6 times per day. In another embodiment, the administration of ornithine and/or aspartate and/or one or more therapeutic agents may continue for less than about 7 days. In yet another embodiment the administration continues for equal or more than about 6, 10, 14, 20, 28, 30 days, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 years. In some cases, continuous dosing is achieved and maintained as long as necessary. In some embodiments, the composition comprising ornithine and/or aspartate administered for at least about a month. In some embodiments, the composition is administered for at least about 10 days. Administration of the composition comprising ornithine and/or aspartate may continue as long as necessary. In some embodiments, a compound of the invention is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, a compound of the invention is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

[0051] The compositions of the invention may be administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen may be desired for optimal therapy. Dosing for a compound of the invention may be found by routine experimentation in light of the instant disclosure.

[0052] Determining an appropriate dosage for administration of a composition comprising ornithine and/or aspartate to a subject may take into account any of a variety of factors, such as those just mentioned, for example, any potential or actual side-effect(s), and/or a purpose of the administration of the composition comprising ornithine and/or aspartate, such as a condition treatment purpose, a reducing side-effect purpose, and/or other purpose(s) for which the composition comprising ornithine and/or aspartate may be administered to a subject. Determining an appropriate dosage may take into account any of these factors, any other suitable factor(s), any side-effect(s), animal study modeling, human study modeling, clinical study modeling, drug study modeling, and any balancing therebetween.

[0053] The amount of ornithine and/or aspartate that can be absorbed by a subject, or the rate of absorption of ornithine and/or aspartate by a subject may vary from subject to subject, based on any of a variety of factors. Examples of such factors include metabolic rate, kidney function, overall health, and/or other factor(s) concerning a subject, and a property or nature of the composition comprising ornithine and/or aspartate itself, such as the counter ion, any enhancing agent, its administration vehicle

or method, and/or other factor(s) concerning the composition comprising ornithine and/or aspartate and/or its administration to a subject.

[0054] The compositions comprising ornithine and/or aspartate according to the invention are effective over a wide dosage range. For example, in the administration to adult humans, dosages from 0.0005 to 100 g, from 0.01 to 100 g, from 0.001 to 50 g, from 0.005 to 30 g per day, and from 0.01 to 20 g per day are non-limiting examples of dosages that may be used. In some embodiments, the dosage can be at least 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10 g. The dosage for administration to adult human can be at least 3 g. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be administered to, the body weight of the subject to be administered to, and the preference and experience of the attending physician.

[0055] It is contemplated that a dosage for administration of ornithine and/or aspartate to a subject may take account the number of molecular entities of ornithine, aspartate, or a combination of both ornithine and aspartate if both are comprised in the composition. It is contemplated that a dosage for administration of ornithine and/or aspartate to a subject may be from about 1.5 mg/kg of body weight/day to about 1 g/kg of body weight/day. For example, it is contemplated that a dosage for administration of ornithine and/or aspartate to a subject may be less than about 0.9 g/kg of body weight/day of ornithine and/or aspartate; may be about 300 mg/kg of body weight/day to about 1 g/kg of body weight/day; and may be about 150 mg/kg of body weight/day to about 300 mg/kg of body weight/day for disease and/or pathological condition treatment purpose(s), such as the treatment of diabetes or hyperglycemia, or side-effects of some anti-hyperglycemic agents, for example. Such amounts may be suitable for a human subject, for example. The dosage for administration of ornithine and/or aspartate to a subject may be less than 150 mg/kg.

[0056] As mentioned above, such a dosage may be determined, modified and/or refined based on any suitable factor(s), such as results of clinical trials concerning subjects, for example human subjects. In some embodiments, a suitable dosage may be determined, modified and/or refined based on a determination of a suitable dosage for a suitable animal model, based on experimental studies or tests, for example, and conversion of such a suitable animal dosage to a suitable human dosage, based on suitable conversion factor(s), such as any suitable established conversion factor(s), for example. Further by way of example, it is contemplated that any such suitable human dosage may be further determined, modified and/or refined based on clinical trials involving human subjects, for example.

[0057] In clinical practice, there are multiple types of anti-hyperglycemic agents that are currently prescribed and administered to a subject that is suffering from hyperglycemia or diabetes. The anti-

hyperglycemic agents may be effective in lowering levels of glucose in the serum or bloodstream. The glucose levels that are lowered may be fasting glucose level or glucose level after a meal, or during a glucose tolerance test. Glucose tolerance test or glucose challenge test is a medical test in which glucose is given and blood samples taken afterward to determine how quickly it is cleared from the blood. The test can be used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia and acromegaly, or rarer disorders of carbohydrate metabolism. The glucose tolerance test can be performed as an oral glucose tolerance test (OGTT), which comprises ingesting a standard dose of glucose by mouth and checking the blood levels two hours later. Many variations of the glucose tolerance test have been devised over the years for various purposes, with different standard doses of glucose, different routes of administration, different intervals and durations of sampling, and various substances measured in addition to blood glucose.

[0058] Current clinical medications for treatment of diabetes act upon the condition by lowering glucose levels in the blood. Therefore, they can be referred as anti-hyperglycemic agents. There are different classes of anti-hyperglycemic agents, and their selection can depend on the nature of the diabetes, age and situation of the person, as well as other factors. Type I diabetes is a disease caused by the lack of insulin. Therefore, insulin or insulin analogues can be used to treat type I diabetes. Type II diabetes is a disease of insulin resistance by cells. Treatments can include administering to the patient agents that increase the amount of insulin secreted by the pancreas, agents that increase the sensitivity of target organs to insulin, or agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract. Several groups of anti-hyperglycemic agents are effective in treating type II diabetes. These anti-hyperglycemic agents can be administered as a single drug therapy or combination therapy.

[0059] The types of the anti-hyperglycemic agents known in the art may include, but are not limited to, HMG-CoA inhibitors (or statins), biguanides, sulfonylureas, thiazolidinediones, meglitinides, glinides, α -glucosidase inhibitors, repaglinide, nateglinide, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin or insulin and insulin analogues. Non-limiting examples of insulin and insulin analogues for use to treat hyperglycemia or diabetes, in particular type I diabetes, can include rapid acting insulins, intermediate acting insulins and long acting insulins. The rapid acting insulin can include regular insulin (Humulin R, Novolin R), insulin lispro (Humalog), insulin aspart (Novolog), insulin glulisine (Apidra), prompt insulin zinc (Semilente) and the like. The intermediate acting insulins can include isophane insulin, neutral protamine hagedorn (Humulin N, Novolin N), insulin zinc (Lente) and the like. The long acting insulins can include extended insulin zinc insulin (Ultralente), insulin glargine (Lantus), insulin detemir (Levemir), and the like. The anti-hyperglycemic agents can be insulin sensitizers. Insulin sensitizers

can be used to treat type II diabetes in particular. The insulin sensitizers can include, but are not limited to biguanides or thiazolidinediones. The biguanides can be Metformin, Phenformin or Buformin. Metformin is usually the first-line medication used for treatment of type II diabetes clinically. The thiazolidinediones can be rosiglitazone (Avandia), pioglitazone (Actos) or troglitazone (Rezulin). The anti-hyperglycemic agents can be agents that increase insulin output from pancreas, such as secretagogues. The secretagogues can be sulfonylureas, or nonsulfonylurea secretagogues. The sulfonylureas can include, but are not limited to: tolutamide (Orinase, Rastinon brand name), acetohexamide (Dymelor), tolazamide (Tolinase), chlorpropamide (Diabinese), glipizide (Glucotrol, Minidiab, Glibenese), glyburide or glibenclamide (Diabeta, Micronase, Glynase, Danil, Euglycon), glimepiride (Amaryl), gliclazide (Uni Diamicon), glycopyramide, gliquidone (Glurenorm). The nonsulfonylurea secretagogues can include meglitinides, repaglinide (Prandin, Novonorm), or nateglinide (Starlix). The anti-hyperglycemic agents or anti-diabetes agents can be alpha glucosidase inhibitors. Alpha glucosidase inhibitors can slow the digestion of starch in the small intestine, so that glucose from the starch of a meal can enter the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. Non-limiting examples of alpha glucosidase inhibitors can include miglitol (Glyset), acarbose (Precose/Glucobay), or voglibose. The anti-hyperglycemic agents can be peptide analogs. The peptide analogs can include but are not limited to: injectable incretin mimetics, injectable glucagon-like peptide analogs and agonists, gastric inhibitory peptide analogs, dipeptidyl peptidase-4 inhibitors, or injectable amylin analogues. The injectable incretin mimetics can include glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). The injectable glucagon-like peptide analogs and agonists can include exenatide (also exendin-4 or Byetta), liraglutide, taspoglutide, or lixisenatide (Lyxumia) sanofi aventis. The dipeptidyl peptidase-4 inhibitors can increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4. The dipeptidyl peptidase-4 inhibitors can include vildagliptin (Galvus), sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta),alogliptin or sepagliptin. The injectable amylin analogues can be pramlintide. The anti-hyperglycemic or anti-diabetes agents can be glycosurics. The glycosurics can be sodium/glucose cotransporter 2 (SGLT2) and it functions to block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine. The glycosurics can be canagliflozin (Invokana) or dapagliflozin (Forxiga). In some cases, the anti-hyperglycemic agents or anti-diabetes agents can be natural substances such as plants, elements or chinese medicine. Non-limiting examples of natural substances as anti-hyperglycemic or anti-diabetes

agents include cinnamon, sandalwood, kino tree, *Gentiana olivieri*, chromium supplements, vanadyl sulfate or thiamine.

[0060] When the one or more therapeutic agents (e.g., anti-hyperglycemic agents or anti-diabetes agents) as described herein is administered in a composition that also comprises ornithine and/or aspartate, the one or more therapeutic agents can be used in an amount that is sub-therapeutic. The sub-therapeutic amount of a therapeutic agent or anti-hyperglycemic agent as described herein can be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99% less than the amount that is considered to be a therapeutic amount when used alone. The therapeutic amount can be a suggested dose by FDA guidelines, or an amount that is assessed for individual subjects or for a group of subjects all having at least one characteristics. The characteristics can be age, weight, race, gender, ethnicity, nationality, a particular diet, physical activity level or a level of certain biomarkers.

[0061] The anti-hyperglycemic agent can be Metformin or Metformin hydrochloride. According to the FDA guideline, the therapeutic dose for Metformin can be around 1000 mg, or 500-2000 mg daily. (metformin hydrochloride extended-release tablets label.

www.accessdata.fda.gov/drugsatfda_docs/label/2008/021574s010lbl.pdf). In some cases, the anti-hyperglycemic agent can be Sitagliptin. The therapeutic amount of Sitagliptin can be less than 100 mg, 50 mg or 25 mg. The therapeutic amount for a subject can be determined or adjusted by a clinician or medical professional. Different amount or dose of the agent can be administered to the subject and the response to the administering can be measured or evaluated. For example without limitation, the fasting serum glucose level or glycosylated hemoglobin level can be measured to determine the therapeutic amount of the anti-hyperglycemic agent (e.g., Metformin or Sitagliptin). A sub-therapeutic amount of the anti-hyperglycemic agent (e.g., Metformin or Sitagliptin) can be any level that is below the recommended dosing of the anti-hyperglycemic agent (e.g., Metformin or Sitagliptin), by FDA guideline or the recommendation of a clinician, or a medical professional such as a patient's physician, nurse, nutritionist, pharmacist, or other health care professional. For example, if a subject's therapeutic amount of Metformin is determined to be 700 mg daily, a dose of 500 mg would be a sub-therapeutic amount. As previously mentioned, the therapeutic amount can be determined for a group of subjects all having at least one characteristics. For example, if the average therapeutic amount of Metformin for subjects that weighs heavier than 300 lbs is 2000 mg, a sub-therapeutic amount can be any amount that is lower than 2000 mg. In some cases, the sub-therapeutic amount of Metformin can be, without limitation, less than about 10, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg. In some cases, the sub-therapeutic

amount of Sitagliptin can be less than about 150, 125, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, or 10 mg.

[0062] A health care professional may include a person or entity that is associated with the health care system. Examples of health care professionals may include surgeons, dentists, audiologists, speech pathologists, physicians (including general practitioners and specialists), physician assistants, nurses, midwives, pharmaconomists/pharmacists, dietitians, therapists, psychologists, physical therapists, phlebotomists, occupational therapists, optometrists, chiropractors, clinical officers, emergency medical technicians, paramedics, medical laboratory technicians, radiographers, medical prosthetic technicians social workers, and a wide variety of other human resources trained to provide some type of health care service

[0063] When the ornithine and/or aspartate is administered in a composition that comprises one or more therapeutic agents (e.g., anti-hyperglycemic agents or anti-diabetes agents), and the therapeutic agents have a shorter half-life than the ornithine and/or aspartate, the unit dose forms of the therapeutic agent and the ornithine and/or aspartate may be adjusted accordingly.

[0064] A composition comprising ornithine and/or aspartate can be formulated to provide an effective amount of ornithine and/or aspartate as the active ingredients, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. The composition can be a pharmaceutical composition. The composition can further comprise one or more therapeutic agents that are selected for their particular usefulness against a condition that is being treated. For example, the therapeutic agent may be an anti-hyperglycemic agent or an anti-diabetes agent. The anti-hyperglycemic agent can be in an amount effective in treating a symptom associated with diabetes. Where desired, the compositions contain pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[0065] A composition comprising ornithine and/or aspartate may be administered to a subject in any suitable manner. Such administration may be oral. Other administration route may be used, such as transdermal, intravenous, aerosol, intramuscular, vaginal, rectal, subdermal, parenteral, ophthalmic, pulmonary, transmucosal, otic, nasal, and topical administration. Components of a composition described herein, such as ornithine-aspartate, at least one agent for increasing the bioavailability or ornithine, or at least one therapeutic agent may be administered to a subject concurrently, such as in any manner of concurrent administration described herein and/or in U.S. Patent Application Publication No.

US 2006/0089335 A1. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[0066] The subject compositions comprising ornithine and/or aspartate can be administered alone or in combination with one or more other agents (e.g., anti-hyperglycemic agents or anti-diabetes agents), which are also typically administered in the form of compositions. Where desired, ornithine and/or aspartate, and other agent(s) may be mixed into a preparation or all components may be formulated into separate preparations to use them in combination separately or at the same time. In some embodiments, the compositions may be in unit dosage form. In some embodiments, the ornithine and/or aspartate and one or more therapeutic agents can be packaged separately or together. The ornithine and/or aspartate may be packaged separately from the one or more therapeutic agents but administered together. The ornithine and/or aspartate may be administered separately from the one or more therapeutic agents.

[0067] In some embodiments, the content of ornithine and/or aspartate provided in the compositions of the present invention is less than about 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w or w/v. In some embodiments, the content of ornithine and/or aspartate in the compositions is greater than about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25%, 19%, 18.75%, 18.50%, 18.25%, 18%, 17.75%, 17.50%, 17.25%, 17%, 16.75%, 16.50%, 16.25%, 16%, 15.75%, 15.50%, 15.25%, 15%, 14.75%, 14.50%, 14.25%, 14%, 13.75%, 13.50%, 13.25%, 13%, 12.75%, 12.50%, 12.25%, 12%, 11.75%, 11.50%, 11.25%, 11%, 10.75%, 10.50%, 10.25%, 10%, 9.75%, 9.50%, 9.25%, 9%, 8.75%, 8.50%, 8.25%, 8%, 7.75%, 7.50%, 7.25%, 7%, 6.75%, 6.50%, 6.25%, 6%, 5.75%, 5.50%, 5.25%, 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 1.25%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w or w/v. In some embodiments, the content of ornithine and/or aspartate in the composition is about 49 %.

[0068] In some embodiments, the amount of ornithine and/or aspartate present in a salt form or free form in the composition is equal to or less than 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9.5, 9, 8.5, 8, 7.5, 7, 6.5, 6, 5.5, 5, 4.5, 4, 3.5, 3, 2.5, 2, 1.5, 1,

0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, 0.01, 0.009, 0.008, 0.007, 0.006, 0.005, 0.004, 0.003, 0.002, 0.001, 0.0009, 0.0008, 0.0007, 0.0006, 0.0005, 0.0004, 0.0003, 0.0002, or 0.0001 g. In some embodiments, the amount of ornithine and/or aspartate in a salt form or free form is more than 0.0001, 0.0002, 0.0003, 0.0004, 0.0005, 0.0006, 0.0007, 0.0008, 0.0009, 0.001, 0.002, 0.003, 0.004, 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 g. In some embodiments, the amount of ornithine and/or aspartate in a salt form or free form is more than 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 g. In some embodiments, the amount of ornithine and/or aspartate in the composition is less than 9 g. In some embodiments, the amount of ornithine and/or aspartate in a salt form or free form in the composition is less than 3 g. In some embodiments, the amount of ornithine and/or aspartate in a salt form or free form in the composition is more than 3 g. In some embodiments, the amount of ornithine and/or aspartate in a salt form or free form in the composition is 0.95 g. In some embodiments, the composition may comprise ornithine and/or aspartate in a salt form or free form in an amount between 0.0001-1, 0.0001-3, 0.0001-2.5, 0.001-2.5, 0.1-2.5, 0.001-3, 0.01-3, 0.1-3, 0.1-20, 0.01-20, 0.01-15, 0.01-10, 0.01-5, 0.01-100, 0.5-3, 0.5-9, 3-9, 0.1-10, 1-3, 1-5 g.

[0069] A composition of the invention typically comprises an active ingredient (e.g., ornithine and/or aspartate) of the present invention or a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including but not limited to inert solid diluents and fillers, diluents, sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. The composition can further comprise one or more supplements or other active ingredients. The composition can further comprise one or more herbal extract. The composition can further comprise one or more coloring pigments.

[0070] Described below are non-limiting exemplary compositions and methods for preparing the same. In some embodiments, the invention provides a pharmaceutical composition for oral administration comprising ornithine and/or aspartate, and a pharmaceutical excipient suitable for oral administration. In some embodiments, the invention provides a solid pharmaceutical composition for oral administration comprising: (i) an effective amount of ornithine and/or aspartate; (ii) an amount of a therapeutic agent (e.g., an anti-hyperglycemic agent or an anti-diabetes agent); optionally (iii) an effective amount of one or more other agents; and (iv) a pharmaceutical excipient suitable for oral administration. In some embodiments, the anti-hyperglycemic or anti-diabetes agent is present in an amount that is sub-

therapeutic in reducing serum glucose level in the subject with hyperglycemia or diabetes if the anti-hyperglycemic or the anti-diabetes agent is administered alone.

[0071] A composition comprising ornithine and/or aspartate appropriate for administration to a subject may be provided in any suitable form, such as a liquid form, a gel form, a semi-liquid (for example, a liquid, such as a viscous liquid, containing some solid) form, a semi-solid (a solid containing some liquid) form, and/or a solid form, for example. Merely by way of example, a tablet form, a capsule form, a food form a chewable form, a non-chewable form, a slow- or sustained-release form, a non-slow- or non-sustained-release form, and/or the like, may be employed. Gradual-release tablets are known in the art. Examples of such tablets are set forth in U.S. Pat. No. 3,456,049. Such a composition may comprise an additional agent or agents, whether active or passive. Examples of such an agent include a sweetening agent, a flavoring agent, a coloring agent, a filling agent, a binding agent, a lubricating agent, an excipient, a preservative, a manufacturing agent, and/or the like, merely by way of example, in any suitable form. A slow- or sustained-release form may delay disintegration and/or absorption of the composition and/or one or more component(s) thereof over a period, such as a relatively long period, for example. A food form may take the form of a food bar, a cereal product, a bakery product, a dairy product, and/or the like, for example. A bakery product form may take the form of a bread-type product, such as a bagel or bread itself, for example, a donut, a muffin, and/or the like, merely by way of example. A component of a composition comprising ornithine and/or aspartate may be provided in a form that is other than that of another component of the composition. For example, ornithine and/or aspartate may be provided in a solid form, such as solid food or cereal that is taken with an anti-hyperglycemic agent in a liquid form. Such administration of compositions comprising ornithine and/or aspartate in multiple forms, may occur simultaneously (e.g., ingesting a tablet of anti-hyperglycemic agent with a ornithine-aspartate-fortified milk), or at different times.

[0072] In some embodiments, the composition comprising ornithine and/or aspartate may be a solid or liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as a discrete or unit dosage form each containing a predetermined amount of an active ingredient. The predetermined amount of the active ingredients may be a powder or granules, beads, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. The subject dosage forms can be prepared by any of the methods of pharmacy. In some cases, the methods may include the step of bringing the active ingredient into association with the carrier, which constitutes one or more desired ingredients. The compositions may be prepared by uniformly and intimately admixing the active

ingredient with liquid carriers or finely divided solid carriers or both, and then, if desired, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Tablets can be compressed by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Tablets can be molded by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0073] This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water may be added (e.g., 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[0074] An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, including but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, granules and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[0075] Binders suitable for use in the subject pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[0076] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, talcum, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[0077] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which may disintegrate in the bottle. Too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, povidone, povidone k30, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums or mixtures thereof.

[0078] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[0079] When the compositions comprising ornithine and/or aspartate are desired for oral administration, the composition therein may be combined with various sweetening or flavoring agents (e.g., aspartame, sugar), coloring matter or dyes (e.g., yellow pigment) and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[0080] Sweeteners, sweetening agents or flavoring agents are substances that sweeten food, beverages, or pharmaceutical compositions. Sweeteners may be sugar, saccharine or other low-calorie synthetic products (From Random House Unabridged Dictionary, 2d ed). Non-limiting examples of the sweetening or flavoring agent include N-(N-(3-(3-hydroxy-4-methoxyphenyl) propyl)-alpha-aspartyl)-L-phenylalanine 1-methyl ester (Aspartame), 11-oxo-mogroside V, aspartyl-alanine fenchyl ester, auburside A methyl ester, neotame, osladin, SC 45647, cellobiofructose, gentiobiofructose, 4,4',6,6'-tetrachloro-4,4',6,6'-tetradeoxygalactotrehalose, brazzein protein, Pentadiplandra brazzeana, hydrangenol-4'-O-glucoside, hydrangenol-8-O-galactoside, 3,3'-dideoxytrehalose, selligieain A, periandrin V, NC 174, mabinlin protein, Capparis masaikai, alitame, cyclocarioside A, mabilin II protein, Capparis masaikai, N-(4-cyanophenyl)-N'-(2-carboxyethyl)urea, steviolbioside, Adentol, periandradulcin C, periandradulcin B, periandradulcin A, Sweetrex, monellin, Asn(22)-Gln(25)-Asn(26)-A-chain-Asn(49)-Glu(50)-B-chain, curculin, leucrose, polypodoside A, rubusoside, glycyrrhetyl 3-monoglucuronide, oxime V, hernandulcin, fungitetraose, neosugar, mogroside IV, mogroside V, mogroside VI, coupling sugar, 4-chlorokynurenine, glucosylsucrose, 6-chlorotryptophan, rebaudioside A, perillartine, hydrangenol, Palatinit, Lycasin, cycloheptylsulfamate, CH 401-Na, neohesperidin dihydrochalcone, P 4000, maltitol, phyllostulcin, miraculin protein, Synsepalum dulcificum, acetosulfam or dulcin.

[0081] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[0082] Surfactant which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic

surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[0083] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[0084] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[0085] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[0086] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides,

cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[0087] Hydrophilic non-ionic surfactants may include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[0088] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[0089] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[0090] In one embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially beneficial for compositions for non-oral use, e.g., compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[0091] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofuro) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ϵ -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, citrate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ϵ -caprolactone and isomers thereof, δ -valerolactone and isomers thereof, β -butyrolactone and isomers thereof, and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, mono-octanoin, diethylene glycol monoethyl ether, and water.

[0092] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcitol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[0093] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a subject using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[0094] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[0095] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-

bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[0096] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

[0097] The composition may further comprise one or more herbs or supplements that are known in the art. Non-limiting examples of the herbs or the supplements may be Acai, Alfalfa, Aloe, Aloe Vera, Aristolochic Acids, Asian Ginseng, Astragalus, Bacillus coagulans, Belladonna, Beta-carotene, Bifidobacteria, Bilberry, Biotin, Bitter Orange, Black Cohosh, Black cohosh, Black psyllium, Black tea, Bladderwrack, Blessed thistle, Blond psyllium, Blueberry, Blue-green algae, Boron, Bromelain, Butterbur, Calcium, Calendula, Cancell/Cantron/Protocel, Cartilage (Bovine and Shark), Cassia cinnamon, Cat's Claw, Chamomile, Chasteberry, Chondroitin sulfate, Chromium, Cinnamon, Clove, Coenzyme Q-10, Colloidal Silver Products, Cranberry, Creatine, Dandelion, Devil's claw, DHEA, Dong quai, Echinacea, Ephedra, Essiac/Flor-Essence, Eucalyptus, European Elder (Elderberry), European Mistletoe, Evening Primrose Oil, Fenugreek, Feverfew, Fish oil, Flaxseed, Flaxseed oil, Folate, Folic acid, Garlic, Ginger, Ginkgo, Ginseng, Glucosamine hydrochloride, Glucosamine sulfate, Goldenseal, Grape Seed Extract, Green Tea, Hawthorn, Hoodia, Horse Chestnut, Horsetail, Hydrazine Sulfate, Iodine, Iron, Kava, Lactobacillus, Laetrile/Amygdalin, L-arginine, Lavender, Licorice, Lycium, Lycopene, Magnesium, Manganese, Melatonin, Milk Thistle, Mistletoe Extracts, Niacin and niacinamide (Vitamin B3), Noni, Oral Probiotics, Pantothenic acid (Vitamin B5), Passionflower, PC-SPES, Pennyroyal, Peppermint, Phosphate salts, Pomegranate, Propolis, Pycnogenol, Pyridoxine (Vitamin B6), Red Clover, Red yeast, Riboflavin (Vitamin B2), Roman chamomile,

Saccharomyces boulardii, S-Adenosyl-L-Methionine (SAME), Sage, Saw Palmetto, Selected Vegetables/Sun's Soup, Selenium, Senna, Soy, St. John's Wort, sweet orange essence, Tea Tree Oil, Thiamine (Vitamin B1), Thunder God Vine, Turmeric, Valerian, Vitamin A, Vitamin B12, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Wild yam, Yohimbe, Zinc or 5-HTP.

[0098] In some embodiments, a composition that may be applicable for oral administration to a subject with hyperglycemia or a diabetes may comprise ornithine-aspartate, citrate, mannitol, povidone k30, sweet orange essence, sunset yellow pigment, aspartame, ethanol, and talcum powder.

[0099] In some embodiments, the invention provides a pharmaceutical composition for injection containing a compound of the present invention and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein. The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00100] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[00101] Sterile injectable solutions are prepared by incorporating the compound of the present invention in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00102] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic

effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[00103] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, e.g., Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., *Basic and Clinical Pharmacology*, Ninth Edition, McGraw Hill, 20037ybg; Goodman and Gilman, eds., *The Pharmacological Basis of Therapeutics*, Tenth Edition, McGraw Hill, 2001; Remingtons Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, *The Extra Pharmacopoeia*, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety.

[00104] In another aspect of the invention, methods for lowering the serum level of glucose and/or reducing side effects of a therapeutic agent (i.e. anti-hyperglycemic agent) with compositions comprising ornithine and/or aspartate are described herein. Methods, compositions and/or the use of ornithine and/or aspartate described herein may be useful for purposes described herein, such as reducing glucose level in the bloodstream or serum of a subject. The subject methods comprising the use of ornithine and/or aspartate may be applicable for administering to a subject that is suffering from hyperglycemia, at risk of suffering from hyperglycemia, and/or suffering from a condition that is associated with hyperglycemia such as diabetes. In some cases, an effective amount of a therapeutic agent that is known in the medical art (e.g., an anti-hyperglycemic agent or anti-diabetes agent) can be administered to a subject in conjunction with an effective amount of ornithine and/or aspartate. In some embodiments, the anti-hyperglycemic agent may induce a side effect. Methods described herein may also be useful for ameliorating the side-effect induced by the anti-hyperglycemic agent. A description of various aspects, features, embodiments, and examples, is provided herein..

[00105] The methods described herein comprise administering to a subject a composition comprising ornithine and/or aspartate. "Subject" refers to an animal, such as a mammal, for example a human. The methods and compositions described herein can be useful in both human therapeutics, pre-

clinical, and veterinary applications. In some embodiments, the subject is a mammal, and in some embodiments, the subject is human. The subject can be at different ages. The human subject can be a child (e.g., a neonate, an infant, a toddler, a preadolescent), an adolescent, a pubescent, or an adult (e.g., an early adult, a middle aged adult, a senior citizen). The human subject can be between about 0 months and about 120 years old, or older. The human subject can be between about 0 and about 12 months old; The human subject can be between about 0 and 12 years old; The human subject can be between about 13 years and 19 years old; for example, about 13, 14, 15, 16, 17, 18, or 19 years old. The human subject can be between about 20 and about 39 year old; for example, about 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, or 39 years old. The human subject can be between about 40 to about 59 years old; for example, about 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59 years old. The human subject can be greater than 59 years old; for example, about 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, or 120 years old. The human subject can be about 45 years old or older. The human subject can be 55 years old or older. The human subject can be a male subject or a female subject.

[00106] The human subject can come from different ethnic groups, geographical regions, countries, continents and races. For example, the human subject can be an Asian (e.g., far-east Asian, middle-east Asian, south-east Asian, north-east Asian, or Asian Indian), a Caucasian (Canadian, American, European, or Mediterranean), an African, a pacific islander, or a Hispanic. The human subject can come from Khoid (Hottentot) race, Sanid (Bushmen) race, Central Congoid race (Geographic center and origin in the Congo river basin), Bambutid race (African Pygmies), Aethiopid race (Ethiopia, Somalia), Mediterranid race (from Mediterranean areas), Dinaric race (predominant in western Balkans [Dinaric Mountains] and northern Italy), Alpine race, Ladogan race (named after Lake Ladoga; indigenous to Russia; includes Lappish subrace of arctic Europe), Nordish or Northern European race, Armenid race (Armenia, Syria, Lebanon and northern Iraq), Turanid race (Kazakhstan, Hungary and Turkey), Irano-Afghan race (Iran and Afghanistan, Iraq, Turkey), Indic or Nordindid race (Pakistan and northern India), Dravidic race (India, Bangladesh and Sri Lanka), Veddoid race (remnant Australoid population in central and southern India) Melanesian race (New Guinea, Papua, Solomon Islands), Australian-Tasmanian race (Australian Aborigines), Northeast Asian or Northern Mogoloid race (China, Manchuria, Korea and Japan), Southeast Asian or Southern Mongoloid race (China, Indochina, Thailand, Myanmar [Burma], Malaysia, Indonesia and the Philippines), Micronesian-

Polynesian race, Ainuid race (remnants of aboriginal population in northern Japan), Tungid race (Mongolia and Siberia, Eskimos), Amerindian race (American Indians). The human subject can come from Afghanistan, Albania, Algeria, Andorra, Angola, Antigua and Barbuda, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Barbados, Belarus, Belgium, Belize, Benin, Bhutan, Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Brunei, Bulgaria, Burkina Faso, Burma, Burundi, Cambodia, Cameroon, Canada, Cape Verde, Central African Republic, Chad, Chile, China, Colombia, Comoros, Congo, Costa Rica, Cote d'Ivoire, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Djibouti, Dominican Republic, East Timor, Ecuador, Egypt, El Salvador, Equatorial Guinea, Eritrea, Estonia, Ethiopia, Fiji, Finland, France, Gabon, Gambia, Georgia, Germany, Ghana, Greece, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Holy See, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kazakhstan, Kenya, Kiribati, Korea, Kosovo, Kuwait, Kyrgyzstan, Laos, Latvia, Lebanon, Lesotho, Liberia, Libya, Liechtenstein, Lithuania, Luxembourg, Macau, Macedonia, Madagascar, Malawi, Malaysia, , Maldives, Mali, Malta, Marshall Islands, Mauritania, , Mauritius, Mexico, Micronesia, Moldova, Monaco, Mongolia, Montenegro, Morocco, Mozambique, Namibia, Nauru, Nepal, Netherlands, Netherlands Antilles, New Zealand, Nicaragua, Niger, Nigeria, North Korea, Norway, Oman, Pakistan, Palau, Palestinian Territories, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Rwanda, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Samoa, San Marino, Sao Tome and Principe, Saudi Arabia, Senegal, Serbia, Seychelles, Sierra Leone, Singapore, Slovakia, Slovenia, Solomon Islands, Somalia, South Africa, South Korea, South Sudan, Spain , Sri Lanka, Sudan, Suriname, Swaziland , Sweden, Switzerland, Syria, Taiwan, Tajikistan, Tanzania, Thailand, Timor-Leste, Togo, Tonga, Trinidad and Tobago, Tunisia, Turkey, Turkmenistan, Tuvalu, , Uganda, Ukraine, United Arab Emirates, United Kingdom, Uruguay, Uzbekistan, Vanuatu, Venezuela, Vietnam, Yemen, Zambia, or Zimbabwe.

[00107] The subject can be on different types of diet. "Diet" refers to the types of food that a subject habitually consumes for a period of time. The period of time may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days; 3, 4, 5, 6, 7 or 8 weeks; 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months; 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 years. In some embodiments, the subject on some types of diet may be at risk of diabetes or hyperglycemia. The methods and composition described herein comprising ornithine and/or aspartate may be administered to the subject. In some embodiments, the subject can be on a high-sugar diet, high-fat diet, high-protein diet, low-fiber diet or a diet that is high in refined-starch. For each type of diet, "high"

refers to a content level that is generally higher than the content in a normal diet that is well known in the art, as described by Food and Drug Administration (“Dietary Guidelines for Americans”, 2010). The subject may be on a diet that can cause elevation of one or more hyperlipidemic risk factor levels. The subject can be on a diet that may cause hyperglycemia or diabetes. The subject may consume alcohol excessively. The subject may be on a diet that is high in dessert. The subject may be on a diet that is high in processed food.

[00108] The subject may have different body weights. The subject may be overweight or obese. Being overweight or obese means the body weight of the subject is above an ideal weight range. The ideal weight range is about 18-25 in body mass index (BMI). The BMI is calculated by the number of weight of the subject in kilograms divided by the square of the number of the height of the subject in meters. The subject may have a BMI that is about 25-30. For example, the subject may have a BMI that is about 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 29.9 or 30. The subject may have a BMI that is higher than about 30. For example, the subject may have a BMI that is about 30.5, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40. The subject may have a BMI that is higher than about 40. The subject may weight more than about 50, 75, 100, 125, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, or 400 lbs.

[00109] The subject may have a habit or may be lack of a habit. “Habit” refers to an activity that is performed by a subject routinely or in a frequency that is higher than normal. In some embodiments, the habit can put the subject at risk of hyperglycemia or diabetes. In some embodiments, the habit can increase glucose level in the bloodstream or serum in the subject. The subject may have a habit of smoking or inhaling smokes. The subject may have a habit of smoking tobacco products, including but are not limited to cigarettes, cigars, or pipes. The subject may be in an environment that contains smoke or second-hand smoke. In some cases, the subject may be at risk of hyperglycemia or diabetes because the subject does not have a habit that can lower the risk of diabetes. For example, the subject may not have a habit of exercising or performing physical activities regularly. The subject may exercise or perform physical activities in a frequency that is lower than normal. The subject may exercise, on average, about once in a week, a month, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, 2, 3, 4, 5, 6, 7, 8, 9, 10 years. The subject may exercise about less than once in a week, a month, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, 2, 3, 4, 5, 6, 7, 8, 9, 10 years. The subject may be immobilized.

[00110] The methods and compositions comprising ornithine and/or aspartate described herein can be used for administering to a subject that is suffering from or at risk at suffering from a condition. The condition that the subject can be suffering from or at risk of suffering from can be hyperglycemia or

a condition that is associated with hyperglycemia. In some embodiments, the condition that is associated with hyperglycemia can be diabetes, drugs, liver disorder, pancreatic disorder, pregnancy, critical illness such as stroke and myocardial infarction, hyperlipidemia, obesity, cardiovascular diseases, or drug associated changes in lipid metabolism such as alcohol consumption, estrogen administration and the like. In some embodiments, the cardiovascular diseases can be coronary artery disease, stroke, hypertension, peripheral vascular disease, heart attack or ischemic heart disease, or congenital heart disease.

[00111] Hyperglycemia or high blood sugar may be characterized by a high level or excessive amount of glucose circulating in the bloodstream, plasma or serum. Hyperglycemia can be characterized by a fasting glucose level that is higher than 100 mg/dl, but symptoms may not start to become noticeable until even higher values such as 250–300 mg/dl. A subject with a consistent range between 100 and 126 mg/dl (American Diabetes Association guidelines) is considered hyperglycemic, while above 126 mg/dl or 7 mmol/l is generally held to have diabetes or hyperglycemia. A subject with a consistent range below 70 mg/dl or 4 mmol/l can be considered hypoglycemic. Chronic levels exceeding 7 mmol/l (125 mg/dl) can produce organ damage. Glucose levels can vary before and after meals, and at various times of day. In general, the normal range of a fasting glucose level for most people can be about 80 to 110 mg/dl. Fasting glucose level generally refers to a serum glucose level that is measured after 8 to 12 hours of fasting, or fasting for 8 hours, 10 hours, 12 hours, 15 hours, 24 hours, or even longer. In fasting adults, normal blood plasma glucose can be lower than 126 mg/dL. Sustained higher levels of blood sugar can cause damage to the blood vessels and to the organs they supply, leading to the complications of diabetes. Hyperglycemia can be measured using any methods known in the medical art including the HbA1c test or glucose tolerance test. The condition that the subject is suffering from or at risk of suffering from can be a condition that is associated with an excessive serum level of glucose in the subject. The subject composition comprising ornithine and/or aspartate may be used to change the serum level of glucose in the subject.

[00112] In some embodiments, the methods and compositions comprising ornithine and/or aspartate can be useful for administering to a subject that is classified according to the guideline to be at a very high risk, high risk, borderline-high risk or near optimal on the serum glucose level for hyperglycemia or diabetes. For example, methods and compositions comprising ornithine and/or aspartate can be used on the subject that has a fasting serum glucose level that is higher than 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 126, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 250, or 300 mg/dL. In some embodiments, ornithine and/or aspartate can be administered to

the subject that has fasting serum glucose level that is about 80-300, 80-250, 80-125, 80-100, 100-300, 100-250, 100-125, 125-300, or 250-300 mg/dL. In some embodiments, ornithine and/or aspartate can be used on the subject that has a fasting serum glucose level that is higher than about 100, 125, or 250 mg/dL.

[00113] In some embodiments, the methods and compositions comprising ornithine and/or aspartate may be useful for administering to a subject in combination with one or more anti-hyperglycemic or anti-diabetes agents. The compositions comprising ornithine and/or aspartate may act upon the condition synergistically with the one or more anti-hyperglycemic agent. Therefore, the amount of the one or more anti-hyperglycemic agent administered to a subject suffering from hyperglycemia can be lowered when administered in conjunction with the composition comprising ornithine and/or aspartate. The amount of the one or more anti-hyperglycemic agents administered in conjunction with the composition comprising ornithine and/or aspartate can be sub-therapeutic. Intake of the one or more hyperglycemic agents may cause one or more side effects.

[00114] Treatments of hyperglycemia and conditions that are associated to hyperglycemia using some of the anti-hyperglycemic agents described herein have been shown to cause multiple side effects. In some embodiments, administration of ornithine and/or aspartate does not cause one or more side effects that are associated with other anti-hyperglycemic agents that are described herein. The lack of these adverse side-effects provides advantages for composition comprising ornithine and/or aspartate for its clinic treatment of hyperglycemia or conditions that are associated with hyperglycemia such as diabetes. The side effects can be: weight gain, hypoglycemia, rhabdomyolysis, myopathy, muscle pain, weakness, gastrointestinal problems, lactic acidosis, vitamin B12 deficiency, glycated hemoglobin, increased risk of cardiovascular diseases, edema, anemia, increased lipoprotein levels, increased triglyceride level, increased risk for cancer, or even increased risk of death. The side-effects of anti-hyperglycemia agents may be more pronounced with higher dosages or chronic administration compared to moderate-dosage or sub-therapeutic dosage and shorter administration period. Evidences of the side-effects from the intake of statins, a type of anti-hyperglycemic agent, are well known in the medical art as reported by Preiss et al., "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis," *Journal of the American Medical Association*, 2011: 305(24):2556-64; and Machan et al., "Age-Related Cataract Is Associated with Type 2 Diabetes and Statin Use," *Optometry & Vision Science*, 2012:89(8):1165-1171. Clinical usages of statins may be limited due to these side-effects. Therefore, combination therapy with compositions comprising ornithine and/or aspartate may be useful in lowering the dosage of anti-hyperglycemic or anti-diabetes agents and

subsequently lowering the side effects associated with the anti-hyperglycemic or anti-diabetes agents when administered alone.

[00115] In some cases, the composition comprising ornithine and/or aspartate can be administered in conjunction with one or more anti-diabetes agents or other diabetes treatment. The other diabetes treatment can include changes in diet, changes in exercise habits, and the like. Compositions comprising ornithine and/or aspartate can treat diabetes synergistically with one or more anti-diabetes agents or other diabetes treatment.

[00116] In one embodiment, the subject that is suffering from a condition or at risk of suffering from a condition may be administered an effective amount of ornithine and/or aspartate. The effective amount may be packaged in the dosage form. The effective amount may be a range of physiologically useful quantity of ornithine and/or aspartate to achieve a desired physiological effect. In some other embodiments, the subject composition comprising ornithine and/or aspartate is effective to lower a physiological level of glucose. In some embodiments, the amount of ornithine and/or aspartate administered to a subject may be effective to lower glucose level in the serum of the subject by at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% or even higher as compared to an initial level of glucose prior to administration of it to a subject. The serum glucose level may be lowered by about 19%-24%, 14%-29%, 12%-35%, 10-40%, 8%-45%, 5%-50%, 2%-60%, or 1%-70%. The glucose level can be a fasting glucose level or in a glucose tolerance test. In some embodiments, the composition comprising ornithine and/or aspartate may be administered in an amount effective in lowering the glucose level from a range of at very high risk to a high risk range, a borderline-high risk range, or a desirable range. The glucose level may be lowered from a high risk range to a borderline-high risk range or a desirable range. The glucose level may be lowered from a borderline-high risk range to a desirable range. The glucose level may be lowered to lower than about 300, 250, 225, 200, 175, 150, 125, 120, 115, 100, 95, 90, 85, or 80 mg/dl.

[00117] Where desired, the selected physiological level of serum glucose after administration of the composition comprising ornithine and/or aspartate may be measured under a fasting condition, e.g., without taking food for at least about 8 hours, 10 hours, 12 hours, 15 hours, 24 hours, or even longer or between 8-12 hours. In some cases, the serum glucose level after administration of the composition

comprising ornithine and/or aspartate may be measured 2 hours after ingestion of glucose, or after a meal.

[00118] In some embodiments, the compositions and methods comprising ornithine and/or aspartate may be useful for ameliorating or reducing one or more side-effects of an anti-hyperglycemic agent. The side-effects that may be reduced by the administration of the composition comprising ornithine and/or aspartate may be weight gain, hypoglycemia, rhabdomyolysis, myopathy, muscle pain, weakness, gastrointestinal problems, lactic acidosis, vitamin B12 deficiency, glycated hemoglobin, increased risk of cardiovascular diseases, edema, anemia, increased lipoprotein levels, increased triglyceride level, increased risk for cancer, or even increased risk of death. In some embodiments, the composition comprising ornithine and/or aspartate may reduce the elevated CPK activity level.

[00119] Methods and compositions comprising ornithine and/or aspartate described herein can also be administered to a subject that is also administered with one or more anti-hyperglycemic agents. In some embodiments, the one or more anti-hyperglycemic agents are administered in an amount effective to lower serum glucose level. In some embodiments, the one or more anti-hyperglycemic agents are administered in an amount effective to result in lowering glucose level. In some embodiments, the one or more anti-hyperglycemic agents may have a side-effect. In another case, the one or more anti-hyperglycemic agents may be administered in a sub-therapeutic level in conjunction with the composition comprising ornithine and/or aspartate to minimize the side effects.

[00120] In some embodiments, the composition comprising ornithine and/or aspartate may further comprise an effective amount of one or more therapeutic agents including anti-hyperglycemic agents or anti-diabetes agents. The methods described herein comprise administering the composition comprising ornithine and/or aspartate, and administration of the one or more therapeutic agents (e.g., anti-hyperglycemic agents or anti-diabetes agents). In some embodiments, the compositions comprising ornithine and/or aspartate may be administered together with the one or more therapeutic agents at the same time in the same route. In some embodiments, the composition comprising ornithine and/or aspartate may be administered separately from the one or more therapeutic agents. In some embodiments, the composition comprising ornithine and/or aspartate and the one or more therapeutic agents may be administered subsequently, with the therapeutic agents first or the ornithine and/or aspartate first. In some embodiments, the composition comprising ornithine and/or aspartate may be administered to a subject in conjunction with one or more therapeutic agents. In some embodiments, the composition comprising ornithine and/or aspartate may be administered at the same administration route with the one or more therapeutic agents. The composition comprising ornithine and/or aspartate may be

administered at a different administration route with the one or more therapeutic agents. For example, the composition comprising ornithine and/or aspartate may be administered orally while the one or more therapeutic agents may be administered via intravenous injection. Each of the one or more therapeutic agents may be administered via the same or different administration routes.

[00121] Furthermore, in some cases, the methods described herein comprise administering the composition comprising ornithine and/or aspartate for the same duration of treatment as the one or more therapeutic agents. For example, the composition comprising ornithine and/or aspartate may be administered for 30 days while the one or more therapeutic agents are administered for 10 days. The subject may be on a treatment with one or more therapeutic agents for a period of time before administering the composition comprising ornithine and/or aspartate.

[00122] Methods and compositions are described herein of administering a composition comprising ornithine and/or aspartate to a subject with a condition and administering one or more therapeutic agents (e.g., anti-hyperglycemic agents or anti-diabetes agents) to the subject, such that the condition of the subject is improved following the administration of the composition comprising ornithine and/or aspartate and the administration of the one or more therapeutic agents. The administration of the composition comprising ornithine and/or aspartate may result in improvement of the condition for greater than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 99%. The administration of the one or more therapeutic agents (e.g., anti-hyperglycemic agents or anti-diabetes agents) may also result in improvement of the condition for greater than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 99%. In some embodiments, the condition is improved for greater than 50%. In some instances, the composition comprising ornithine and/or aspartate and the one or more therapeutic agents may act upon the condition synergistically. In some instances, the improvement of the condition after the delivery of both the composition comprising ornithine and/or aspartate and the one or more therapeutic agents is greater than the improvement from treating the subject with the composition comprising ornithine and/or aspartate alone or with the one or more therapeutic agents alone. The improvement may be characterized by the level of biomarkers or risk factors in the subject. The improvement may also be characterized by the functional improvement of an organ in comparison to its normal function.

[00123] Example 1: Formulation and manufacturing process for ornithine-aspartate tablets

[00124] The composition comprising ornithine-aspartate can be formulated and processed to be in a tablet form. The manufacturing process of the ornithine-aspartate tablet is described herein. An example of formulation is shown in Table 1.

[00125] Mix 302.7 g of providence k, 0.5 g of sweet orange essence, and 0.0025 g of sunset yellow pigment with 135 g of 80 % ethanol. Sonicate the mixture briefly and the mixture can be made into an adhesive. Separately, mix 150 g of ornithine-aspartate, 7.5 g of citric acid, 105 g of mannitol and 2.5 g of aspartame together thoroughly. Then, the adhesive mixture is added into the mixture containing ornithine-aspartate, and mixed thoroughly to obtain a soft material. The soft material can be dried, granulated and passed through a 18 mesh sieve. Afterwards, 5 g of talcum powder is added and mixed thoroughly. The mixture can be pressed to then form tablets.

Table 1: Formulation for ornithine-aspartate tablets	
Ornithine aspartate	150 g
Citrate	7.5 g
Mannitol	105 g
Povidone k	302.7 g
Sweet orange essence	0.5 g
Sunset yellow pigment	0.0025 g
Aspartame	2.5 g
80 % Ethanol	135 g
Talcum powder	5 g

[00126] Example 2: Formulation and manufacturing process for ornithine-aspartate capsules

[00127] The composition comprising ornithine-aspartate can be formulated and processed to be in a capsule form. The manufacturing process of the ornithine-aspartate capsules is described herein. An example of formulation is shown in Table 2.

[00128] Mix 302.7 g of povidone k, 0.5 g of sweet orange essence, and 0.0025 g of sunset yellow pigment with 135 g of 80 % ethanol. Sonicate the mixture briefly and the mixture can be made into an

adhesive. Separately, mix 150 g of ornithine-aspartate, 7.5 g of citric acid, 105 g of mannitol and 2.5 g of aspartame together thoroughly. Then, the adhesive mixture is added into the mixture containing ornithine-aspartate, and mixed thoroughly to obtain a soft material. The soft material can be dried, granulated and passed through a 18 mesh sieve. Afterwards, 5 g of talcum powder is added and mixed thoroughly. The mixture is then used to fill capsules to form ornithine-aspartate capsules.

Table 2: Formulation for ornithine-aspartate capsules	
Ornithine aspartate	150 g
Citrate	7.5 g
Mannitol	105 g
Povidone k	302.7 g
Sweet orange essence	0.5 g
Sunset yellow pigment	0.0025 g
Aspartame	2.5 g
80 % Ethanol	135 g
Talcum powder	5 g

[00129] Example 3: Formulation and manufacturing process for ornithine-aspartate granules

[00130] The composition comprising ornithine-aspartate can be formulated and processed to be in a granule form. The manufacturing process of the ornithine-aspartate granules is described herein. An example of formulation is shown in Table 3.

[00131] Mix 302.7 g of povidone k, 0.5 g of sweet orange essence, and 0.0025 g of sunset yellow pigment with 135 g of 80 % ethanol. Sonicate the mixture briefly and the mixture can be made into an adhesive. Separately, mix 150 g of ornithine-aspartate, 7.5 g of citric acid, 105 g of mannitol and 2.5 g of aspartame together thoroughly. Then, the adhesive mixture is added into the mixture containing ornithine-aspartate, and mixed thoroughly to obtain a soft material. The soft material can be dried, granulated and passed through a 12 and a 60 mesh sieve. Afterwards, 5 g of talcum powder is added and mixed thoroughly to form granules. The granules matched the standards can be packed.

Table 3: Formulation for ornithine-aspartate granules	
Ornithine aspartate	150 g
Citrate	7.5 g
Mannitol	105 g
Povidone k	302.7 g
Sweet orange essence	0.5 g
Sunset yellow pigment	0.0025 g
Aspartame	2.5 g
80 % Ethanol	135 g
Talcum powder	5 g

[00132] Example 4: Effects of ornithine-aspartate on blood sugar level in Wistar rats

[00133] The use of a composition comprising ornithine and/or aspartate as described herein is investigated, wherein the composition comprises ornithine-aspartate salt. The composition may treat a subject that is suffering from hyperglycemia or diabetes, and lower serum glucose levels in the subject after administration to the subject the composition, and this effect is investigated herein.

[00134] Male Wistar rats, each weighs about 200-250 g, were housed in groups of six in a temperature (about $23 \pm 1^\circ\text{C}$)- and humidity- controlled environment (about 50~60%) with about 12 hours of light and dark cycle (lights on 07:00 am). The rats were provided free access to food and water. The animals were housed following a clean house-keeping practice, and each rat was weighed once daily. All rats were maintained in this condition for at least one week before experiment commencing.

[00135] Diabetes was induced by administering Streptozotocin (STZ) to the rats following a standard protocol. After establishing successfully the diabetes model, the rats were given ornithine-aspartate (QR0007) via oral administration. Control group was STZ treated diabetes model rats, and was given 4 ml/kg of saline solution for 4 weeks. Treatment group was STZ treated diabetes model rats administered with 312.5 mg/kg of ornithine-aspartate in 4 ml/kg for 4 weeks. The 312.5 mg/kg daily on the animal is equivalent to a 3 g/day clinical dosage to human. The control and treatment groups were administered orally once a day, for 4 weeks continuously.

[00136] After fasting for 12 hours, blood samples of the fasting rats in all groups were obtained from tails of the rats at day 0, week 2, week 3 and week 4 after the administration of saline or ornithine-aspartate. The serum/plasma level of glucose was measured.

[00137] Experimental results showed that QR0007 can control the serum glucose level in rats. In the control group, fasting serum glucose level continued to increase over 4 weeks of time. Compared to the control group, the fasting serum glucose level in the treatment group was significantly lowered at week 2 to week 4 (Table 4, $p < 0.01$, v.s. control). Compared to day 0, QR0007 successfully decreased the fasting serum glucose level over time, with 4.54 mmol/L, 5.00 mmol/L and 3.68 mmol/L of the decrease at week 2, 3 and 4 respectively. The decrease of glucose level was about 30.2%, 33.3% and 24.1% as compared to day 0 (Table 4).

Table 4. Glucose Level (mmol/L) with QR0007 Administration (mean $\pm$ sem, n=7) , ANNOVA followed by Dunnett's test, ** $p < 0.01$, treatment vs. control groups

	Day 0	Week 2	Week 3	Week 4
Control	15.00 $\pm$ 2.99	16.97 $\pm$ 1.31	17.08 $\pm$ 1.59	20.26 $\pm$ 3.78
QR0007 Treatment	15.03 $\pm$ 1.73	10.49 $\pm$ 3.01**	10.03 $\pm$ 2.46**	11.35 $\pm$ 2.94**

[00138] An oral glucose tolerance test (OGTT) was also conducted to assess the glucose tolerance level of the rats. Rats from both control and treatment groups were administered orally 2 g/kg of glucose solution. Blood samples of the rats in all groups were obtained from tail vein at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the administration of glucose solution. The serum/plasma level of glucose was measured.

[00139] As shown in Table 5 and Figure 1, after administering to the rats 2 g/kg of glucose solution, a peak of serum glucose level increase was observed after 0.5 hour in both control and treatment groups. The glucose level subsequently decreased from 0.5 to 2 hours. At all time points, serum glucose levels of the control group were higher than that of the treatment group. As compared to 0 hour, the glucose level after 2 hours increased 8.83 mmol/L and 6.68 mmol/L in the control and treatment groups, respectively. Based on the results of the study, it can be concluded that QR0007 is capable of improving the glucose tolerance of the rats.

Table 5. OGTT Glucose Level (mmol/L) with QR0007 Administration (mean $\pm$ sem, n=7)

	0 hour	0.5 hour	1 hour	2 hours
Control	20.26 $\pm$ 3.78	35.27 $\pm$ 4.68	32.72 $\pm$ 3.82	29.09 $\pm$ 3.48
QR0007 Treatment	11.35 $\pm$ 2.94	25.60 $\pm$ 2.33	22.66 $\pm$ 4.21	18.03 $\pm$ 3.51

[00140] Example 5: Effects of ornithine-aspartate on blood sugar level in SD rats

[00141] The use of a composition comprising ornithine and/or aspartate as described herein is investigated, wherein the composition comprises ornithine-aspartate salt. The composition may treat a subject that is suffering from hyperglycemia or diabetes, and lower serum glucose levels in the subject after administration to the subject the composition, and this effect is investigated herein.

[00142] Male SD rats, each weighs about 200-250 g, were housed in groups of six in a temperature (about $23 \pm 1^{\circ}\text{C}$)- and humidity- controlled environment (about 50~60%) with about 12 hours of light and dark cycle (lights on 07:00 am). The rats were provided free access to food and water. The animals were housed following a clean house-keeping practice, and each rat was weighed once daily. All rats were maintained in this condition for at least one week before experiment commencing.

[00143] Diabetes was induced by administering Streptozotocin (STZ) to the rats following a standard protocol. After successfully establishing the diabetes model, the rats were divided into 5 groups. Control group was STZ treated diabetes model rats (DM model control), and was given 4 ml/kg p.o. of saline solution for 4 weeks. Positive control group was given 100 mg/kg p.o. Metformin (Met) for 4 weeks. Three different dosages of ornithine-aspartate (QR0007) were tested. Low dosage group was STZ treated diabetes model rats administered with 50 mg/kg of ornithine-aspartate in 4 ml/kg for 4 weeks. The 50 mg/kg daily on the animal is equivalent to a 0.5 g/day clinical dosage to human. Mid dosage group was STZ treated diabetes model rats administered with 100 mg/kg of ornithine-aspartate in 4 ml/kg for 4 weeks. The 100 mg/kg daily on the animal is equivalent to a 1 g/day clinical dosage to human. High dosage group was STZ treated diabetes model rats administered with 300 mg/kg of ornithine-aspartate in 4 ml/kg for 4 weeks. The 300 mg/kg daily on the animal is equivalent to a 3 g/day clinical dosage to human. In addition, a group of wild type rats was administered 4 ml/kg p.o. of saline solution for 4 weeks as well without STZ treatment. All groups were administered orally once a day, for 4 weeks continuously.

[00144] After fasting for 12 hours, blood samples of the fasting rats in all groups were obtained from tails of the rats at week 0 (prior to administration), week 1, week 2, week 3 and week 4 after the administration of saline or drug. The serum/plasma level of glucose was measured. An oral glucose tolerance test (OGTT) was also conducted to assess the glucose tolerance level of the rats. Rats from all groups were administered orally 2 g/kg of glucose solution. Blood samples of the rats in all groups were obtained from tail vein at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the administration of glucose solution. The serum/plasma level of glucose was measured.

[00145] As shown in Figure 2, after 4 weeks of treatment, both Metformin and high dose of QR0007 decreased the serum glucose level significantly as compared to the DM model control group (p=0.008 and 0.006 for Metformin and high dose of QR0007 respectively). Both Metformin and high dose of QR0007 showed comparable effects on modulating and decreasing glucose level. As compared to the base line (0 week), the fasting glucose level of the high dose QR0007 group has decreased 5.8 mmol/L, 6.5 mmol/L, 4.2 mmol/L and 4.5 mmol/L at week 1, 2, 3 and 4, respectively. The decrease of glucose level was about 24.5%, 27.4%, 17.7% and 19.0% at week 1, 2, 3 and 4, respectively, as compared to week 0 (Figure 2).

Table 5. OGTT Glucose Level (mmol/L) with QR0007 Administration in low, mid and high dosages (mean±sem, n=6-8), ANNOVA followed by Dunnett's test, **p<0.01, treatment vs. DM control groups

	0 hr	0.5 hr	1 hr	2 hr
Wild Type	4.63±0.78	6.34±0.96	7.48±1.07	5.03±0.94
DM Model Control	26.87±4.25	37.20±3.19	37.30±5.73	30.44±2.76
Positive Control (Metformin)	11.15±4.94**	16.07±4.70**	17.76±4.03**	11.77±2.83**
Low Dose of QR0007	16.68±5.97	23.67±7.70	27.47±6.66	22.15±3.30
Mid Dose of QR0007	17.20±3.73	28.76±4.73	25.87±4.57	21.43±5.03
High Dose of QR0007	9.31±3.22**	17.60±3.86**	18.72±3.82**	16.49±2.79**

[00146] As shown in Table 5, after orally administering 2 g/kg of glucose solution, all groups showed an increase in the serum glucose level. Other than the mid-dosage group, all the other groups showed a peak of glucose level increase after 1 hour. After 2 hours, all groups showed an observable drop in the serum glucose level. Especially in the Metformin group and the high dose of QR0007 group, the serum glucose level showed the most decrease as compared to other groups after 2 hours. A dose-dependent effects of the QR0007 on the decrease in serum glucose level was observed. The DM model control group showed the highest serum glucose level in all groups.

[00147] Based on the results of the study, we conclude that ornithine-aspartate is capable of improving the glucose tolerance of the rats, and the effect is dose-dependent. Ornithine-aspartate in 300 mg/kg p.o. (3 g/day clinically) showed similar effects as Metformin in lowering the serum glucose level in rats.

[00148] Example 6: Combined treatment of ornithine-aspartate and Merformin or Sitagliptin on BKS-DB mice

[00149] The use of a composition comprising ornithine and/or aspartate as described herein with one or more anti-hyperglycemic agents is investigated, wherein the composition comprises ornithine-aspartate salt. The composition may lower the serum glucose level in a subject synergistically with the one or more anti-hyperglycemic agent, and this effect is investigated herein.

[00150] A diabetes mouse model, BKS-DB mice, were acquired for the study. The mice were housed in groups of six in a temperature (about $23 \pm 1^\circ\text{C}$)- and humidity- controlled environment (about 50~60%) with about 12 hours of light and dark cycle (lights on 07:00 am). The mice were provided free access to food and water. The animals were housed following a clean house-keeping practice, and each mouse was weighed once daily. All mice were maintained in this condition for at least one week before experiment commencing.

[00151] The rats were divided into 7 groups (n=6). All groups were administered 10 ml/kg of saline or drug solution orally once a day (around 9-10 am everyday), for 4 weeks continuously. DM model control group was KBS-DB mice administered 10 mg/kg of saline solution. Metformin group (Met) was given 170 mg/kg of Metformin for 4 weeks. Sitagliptin group (Sit) was given 17 mg/kg of Sitagliptin for 4 weeks. The 17 mg/kg of Sitagliptin daily on the mouse is equivalent to a 100 mg/day clinical dosage to human. Ornithine-aspartate (QR0007) group was administered with 300 mg/kg of ornithine-aspartate for 4 weeks. The 300 mg/kg daily on the animal is equivalent to a 3 g/day clinical dosage to human. QR0007+Metformin group was administered with 300 + 170 mg/kg of the drug, respectively. QR0007+ Sitagliptin group was administered with 300 + 17 mg/kg of the drug, respectively. In addition, a group of wild type mice without the diabetes gene mutation was administered 10 ml/kg of saline solution for 4 weeks as well.

[00152] All mice were monitored closely for the amount of water and food consumed, amount of urine, general mental state, activity and hair color. All mice were weighed once weekly. After fasting for 12 hours, blood samples of the fasting mice in all groups were obtained from tail vein at week 0 (prior to drug administration), week 1, week 2, week 3 and week 4 after the administration of saline or drug. The fasting serum/plasma level of glucose was measured. An oral glucose tolerance test (OGTT) was also conducted to assess the glucose tolerance level of the mice after 4 weeks. Mice from all groups were administered orally 2 g/kg of glucose solution. Blood samples of the mice in all groups were obtained from tail vein at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the

administration of glucose solution. The serum/plasma level of glucose was measured. Statistical analysis was performed using SPSS17.0 software. One-way ANNOVA and pair-wise comparison was performed using LSD method. Results were shown in mean $\pm$ sem. Statistically significant difference was shown in * $p<0.05$, ** $p<0.01$.

[00153] Experimental results showed that after administration for 4 weeks, all groups receiving drug administration showed significantly lower fasting serum glucose level, indicating that all drugs are effective in lower fasting serum glucose level and controlling blood sugar level (Figure 3, Table 6). In addition, pair-wise comparison results indicated that although all single drug treatment groups showed lower fasting serum glucose level as compared to the DM model control group, however, combined treatment groups Met+QR0007 and Sit+QR0007 showed much greater effects (Figure 3, Table 6). The percentages of serum glucose level drop in Met+QR0007 and Sit+QR0007 groups were 34.39% and 37.64%, respectively. This result demonstrated that ornithine-aspartate can lower the serum glucose level synergistically with Metformin or Sitagliptin.

Table 6. Glucose Level (mmol/L) with combined therapy of QR0007 and anti-hyperglycemic agents administration in BKS-DB mice over time (mean $\pm$ sem, n=6); ANNOVA followed by Dunnett's test, * $p<0.05$; ** $p<0.01$, treatment vs DB model control group

	0 week	1 week	2 weeks	3 weeks	4 weeks
Wild Type	7.80 $\pm$ 0.65	6.56 $\pm$ 1.03	5.34 $\pm$ 0.57	4.89 $\pm$ 0.44	6.77 $\pm$ 0.73
DB Model Control	17.03 $\pm$ 5.38	17.78 $\pm$ 4.84	22.17 $\pm$ 3.33	22.58 $\pm$ 5.78	26.02 $\pm$ 3.37
Met	16.58 $\pm$ 6.48	17.52 $\pm$ 5.50	18.12 $\pm$ 6.12	17.13 $\pm$ 7.58	16.15 $\pm$ 6.21**
Sit	17.14 $\pm$ 6.62	18.37 $\pm$ 3.68	18.13 $\pm$ 3.27	16.28 $\pm$ 3.21*	15.65 $\pm$ 4.96**
QR0007	17.55 $\pm$ 4.57	19.12 $\pm$ 4.54	18.72 $\pm$ 3.44	16.30 $\pm$ 5.02*	16.45 $\pm$ 5.40**
QR0007+Met	17.30 $\pm$ 6.80	15.05 $\pm$ 3.45	15.17 $\pm$ 1.85**	13.72 $\pm$ 3.82**	11.35 $\pm$ 3.15**
QR0007+Sit	16.63 $\pm$ 5.86	15.52 $\pm$ 4.38	13.13 $\pm$ 2.77**	11.23 $\pm$ 3.16**	10.37 $\pm$ 2.17**

[00154] After orally administering 2 g/kg of glucose solution, all groups showed an increase in the serum glucose level, a peak of glucose level increase after 0.5 hour was observed in all groups. After 2 hours, all groups showed an observable drop in the serum glucose level as compared to 0.5 hour.

Significantly greater decrease in serum glucose level was observed in Sit group, QR0007+Met and QR0007+Sit groups. Based on the results, we conclude that QR0007 and its combined therapy with anti-hyperglycemic agents such as Met and Sit are effective in glucose tolerance. Pair-wise comparison result also indicated that the serum glucose level in both Sit and QR0007+Sit groups dropped significantly after 1 hour already, and the level was maintained after 2 hours, demonstrating that Sit and combined therapy of Sit with ornithine-aspartate can rapidly and effectively lower serum glucose level.

[00155] Based on the results of the study, we conclude that ornithine-aspartate and the combined administration of ornithine-aspartate with anti-hyperglycemic agents such as Metformin and Sitagliptin are capable of lowering serum glucose level and improving the glucose tolerance of the BKS-DB mice, and the effect is synergistic. Ornithine-aspartate combined with Metformin and Sitagliptin demonstrated higher glucose tolerance, but Sitagliptin combined with ornithine-aspartate can further rapidly decrease serum glucose level and treat the condition more effectively.

[00156] **Example 7: Dose-dependent effects on combined treatment of ornithine-aspartate and Merformin**

[00157] The use of a composition comprising ornithine and/or aspartate as described herein with anti-hyperglycemic agent Metformin (Met) is investigated. The composition may lower the serum glucose level in a subject synergistically with the one or more anti-hyperglycemic agent, and this effect may be dose-dependent. The synergistic effect with different doses is investigated herein.

[00158] A diabetes rodent model, BKS-DB mice, are acquired for the study. The animals are housed in groups of six in a temperature (about $23 \pm 1^\circ\text{C}$)- and humidity- controlled environment (about 50~60%) with about 12 hours of light and dark cycle (lights on 07:00 am). The animals are provided free access to food and water. The animals are housed following a clean house-keeping practice, and each animal is weighed once daily. All animals are maintained in this condition for at least one week before experiment commencing.

[00159] The animals are divided into 6 groups. All groups are administered saline or drug solution orally once a day, for 4 weeks continuously. Control group is DM model control group administered with saline solution. Treatment groups includes QR0007 50 mg/kg, p.o. + Met 170 mg/kg, p.o.; QR0007 100 mg/kg, p.o. + Met 170 mg/kg, p.o.; QR0007 300 mg/kg, p.o. + Met 170 mg/kg, p.o.; Saline+Met 170 mg/kg, p.o.. In addition, a group of wild type rodent without the diabetes symptom is administered saline solution for 4 weeks as well.

[00160] All animals are monitored closely for the amount of water and food consumed, amount of urine, general mental state, activity and hair color. All animals are weighed once weekly. After fasting for 12 hours, blood samples of the fasting animals in all groups are obtained from tail vein at week 0 (prior to drug administration), week 1, week 2, week 3 and week 4 after the administration of saline or drug. The fasting serum/plasma level of glucose is measured. An oral glucose tolerance test (OGTT) is also conducted to assess the glucose tolerance level of the animals after 4 weeks. Animals from all groups are administered glucose solution orally. Blood samples in all groups are obtained from tail vein at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the administration of glucose solution. The serum/plasma level of glucose is measured. Statistical analysis can be performed using SPSS17.0 software. One-way ANOVA and pair-wise comparison can be performed using LSD method.

[00161] It is expected that synergistic effects of ornithine-aspartate with the anti-hyperglycemic agent Metformin are observed, and the effects in lowering serum glucose level and glucose tolerance are dose-dependent.

[00162] **Example 8: Dose-dependent effects on combined treatment of ornithine-aspartate and Sitagliptin**

[00163] The use of a composition comprising ornithine and/or aspartate as described herein with anti-hyperglycemic agent Sitagliptin (Sig) is investigated. The composition may lower the serum glucose level in a subject synergistically with the one or more anti-hyperglycemic agent, and this effect may be dose-dependent. The synergistic effect with different doses is investigated herein.

[00164] A diabetes rodent model, BKS-DB mice, are acquired for the study. The animals are housed in groups of six in a temperature (about $23 \pm 1^{\circ}\text{C}$)- and humidity- controlled environment (about 50~60%) with about 12 hours of light and dark cycle (lights on 07:00 am). The animals are provided free access to food and water. The animals are housed following a clean house-keeping practice, and each animal is weighed once daily. All animals are maintained in this condition for at least one week before experiment commencing.

[00165] The animals are divided into 6 groups. All groups are administered saline or drug solution orally once a day, for 4 weeks continuously. The groups include DM model control group administered with saline solution, treatment groups including QR0007 50 mg/kg, p.o. + Sig 17 mg/kg, p.o.; QR0007 100 mg/kg, p.o. + Sig 17 mg/kg, p.o.; QR0007 300 mg/kg, p.o. + Sig 17 mg/kg, p.o.;

Saline+Sig 17 mg/kg, p.o.. In addition, a group of wild type rodent without the diabetes symptom is administered saline solution for 4 weeks as well.

[00166] All animals are monitored closely for the amount of water and food consumed, amount of urine, general mental state, activity and hair color. All animals are weighed once weekly. After fasting for 12 hours, blood samples of the fasting animals in all groups are obtained from tail vein at week 0 (prior to drug administration), week 1, week 2, week 3 and week 4 after the administration of saline or drug. The fasting serum/plasma level of glucose is measured. An oral glucose tolerance test (OGTT) is also conducted to assess the glucose tolerance level of the animals after 4 weeks. Animals from all groups are administered glucose solution orally. Blood samples in all groups are obtained from tail vein at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the administration of glucose solution. The serum/plasma level of glucose is measured. Statistical analysis can be performed using SPSS17.0 software. One-way ANOVA and pair-wise comparison can be performed using LSD method.

[00167] It is expected that synergistic effects of ornithine-aspartate with the anti-hyperglycemic agent Sitagliptin are observed, and the effects in lowering serum glucose level and glucose tolerance are dose-dependent.

[00168] **Example 9: Effects of high doses of ornithine-aspartate on serum glucose level**

[00169] The use of a composition comprising ornithine and/or aspartate as described herein on lowering serum glucose level is investigated. The composition comprising ornithine-aspartate may lower the serum glucose level in a subject in a dose-dependent fashion. The effect with high doses is investigated herein.

[00170] A diabetes rodent model, BKS-DB mice, are acquired for the study. The animals are housed in groups of six in a temperature (about $23 \pm 1^{\circ}\text{C}$)- and humidity- controlled environment (about 50~60%) with about 12 hours of light and dark cycle (lights on 07:00 am). The animals are provided free access to food and water. The animals are housed following a clean house-keeping practice, and each animal is weighed once daily. All animals are maintained in this condition for at least one week before experiment commencing.

[00171] The animals are divided into 6 groups. All groups are administered saline or drug solution orally once a day, for 4 weeks continuously. The groups include DM model control group administered with saline solution, ornithine-aspartate group administered with different dosages of

ornithine-aspartate that are 0.5, 1.0, 1.5 and 3.0 g/kg, p.o. In addition, a group of wild type animals without the diabetes symptom is administered saline solution for 4 weeks as well.

[00172] All animals are monitored closely for the amount of water and food consumed, amount of urine, general mental state, activity and hair color. All animals are weighed once weekly. After fasting for 12 hours, blood samples of the fasting animals in all groups are obtained from tail vein at week 0 (prior to drug administration), week 1, week 2, week 3 and week 4 after the administration of saline or drug. The fasting serum/plasma level of glucose is measured. An oral glucose tolerance test (OGTT) is also conducted to assess the glucose tolerance level of the animals after 4 weeks. Animals from all groups are administered glucose solution orally. Blood samples in all groups are obtained from tail vein at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the administration of glucose solution. The serum/plasma level of glucose is measured. Statistical analysis can be performed using SPSS17.0 software. One-way ANOVA and pair-wise comparison can be performed using LSD method.

[00173] It is expected that a dose-dependent effects of ornithine-aspartate are observed.

[00174] **Example 10: Combined treatment of ornithine-aspartate and one or more hyperglycemic agents**

[00175] The use of a composition comprising ornithine and/or aspartate as described herein with one or more anti-hyperglycemic agents other than biguanides or DPP-IV inhibitor is investigated, wherein the composition comprises ornithine-aspartate salt. The composition may lower the serum glucose level in a subject synergistically with the one or more anti-hyperglycemic agent, and lowering the side effects of the one or more anti-hyperglycemic agents. The effects are investigated herein.

[00176] A diabetes rodent model, BKS-DB mice, is acquired for the study. The animals are housed in groups of six in a temperature (about $23 \pm 1^\circ\text{C}$)- and humidity- controlled environment (about 50~60%) with about 12 hours of light and dark cycle (lights on 07:00 am). The animals are provided free access to food and water. The animals are housed following a clean house-keeping practice, and each animal is weighed once daily. All animals are maintained in this condition for at least one week before experiment commencing.

[00177] The animals are divided into different groups (n=6 or more). All groups are administered saline or drug solution orally once a day, for 4 weeks continuously. The groups include DM model control group administered with saline solution, ornithine-aspartate group administered with different dosages of ornithine-aspartate, sulfonylureas group, glinides group, thiazolidinediones group, α -

glucosidase inhibitor group and combined treatment groups with different dosages. In addition, a group of wild type rodent without the diabetes symptom is administered saline solution for 4 weeks as well. The dosages of each of the anti-hyperglycemic agents include both clinically equivalent therapeutic dosage when the agent is administered alone and sub-therapeutic dosages.

[00178] All animals are monitored closely for the amount of water and food consumed, amount of urine, general mental state, activity and hair color. All animals are weighed once weekly. After fasting for 12 hours, blood samples of the fasting animals in all groups are obtained from tail vein at week 0 (prior to drug administration), week 1, week 2, week 3 and week 4 after the administration of saline or drug. The fasting serum/plasma level of glucose is measured. An oral glucose tolerance test (OGTT) is also conducted to assess the glucose tolerance level of the animals after 4 weeks. Animals from all groups are administered glucose solution orally. Blood samples in all groups are obtained from tail vein at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the administration of glucose solution. The serum/plasma level of glucose is measured. Side effects of the anti-hyperglycemic agents are monitored. Statistical analysis can be performed using SPSS17.0 software. One-way ANOVA and pair-wise comparison can be performed using LSD method.

[00179] It is expected that synergistic effects of ornithine-aspartate with the anti-hyperglycemic agents are observed, and the effects in lowering serum glucose level and glucose tolerance are dose-dependent. It is also expected that side-effects of the anti-hyperglycemic agents can be reduced in the combined treatment groups with sub-therapeutic dosages of the anti-hyperglycemic agents.

[00180] **Example 11: Effects of ornithine-aspartate on serum glucose level in human**

[00181] The use of a composition comprising ornithine and/or aspartate as described herein on lowering serum glucose level is investigated. The composition comprising ornithine-aspartate and combination of ornithine-aspartate with one or more anti-hyperglycemic agents may lower the serum glucose level in a human in a dose-dependent fashion. The effect is investigated herein.

[00182] A group of diabetes patients are enrolled for the study. All patients have similar diet and exercise habits, ages and/or weights. The weight of each patient is monitored daily.

[00183] The patients are divided into different groups (n=6 or more for each group). All groups are administered saline or drug solutions orally for at least 4 weeks. The groups include placebo control group administered with only saline solution, ornithine-aspartate group, anti-hyperglycemic agent group, and combination group with ornithine-aspartate and one or more anti-hyperglycemic agents. Different

dosages of anti-hyperglycemic agents may be tested and the dosages can be therapeutic or sub-therapeutic.

[00184] All patients are asked to record the amount of water and food consumed, amount of urine, general mental state, and activity daily. After fasting for 8-12 hours, blood samples of the fasting patients in all groups are obtained at week 0 (prior to drug administration), week 1, week 2, week 3 and week 4 after the administration of saline or drug. The fasting serum/plasma level of glucose is measured. An oral glucose tolerance test (OGTT) is also conducted to assess the glucose tolerance level after 4 weeks. All patients are administered glucose solution orally. Blood samples in all groups are obtained at time 0 (prior to glucose administration), 0.5 hour, 1 hour and 2 hours after the administration of glucose solution. The serum/plasma level of glucose is measured. Side effects of the anti-hyperglycemic agents are monitored. Statistical analysis can be performed using SPSS17.0 software. One-way ANOVA and pair-wise comparison can be performed using LSD method.

[00185] It is expected that ornithine-aspartate and the combined therapy are capable of lowering serum glucose level and glucose tolerance in human. In addition, combined therapy with sub-therapeutic amount of anti-hyperglycemic agents can reduce the side effects of the anti-hyperglycemic agents.

[00186] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby

CLAIMS

WHAT IS CLAIMED IS:

1. A method of lowering serum glucose level in a subject with hyperglycemia, comprising:
 - (a) identifying a subject suffering from hyperglycemia, wherein the subject has a serum glucose level of higher than about 100 mg/dL after fasting for about 8 to 12 hours;
 - (b) administering to said subject a composition comprising ornithine and/or aspartate in an amount that is effective in lowering the serum glucose level.
2. The method of claim 1, wherein at least a portion of said ornithine (O) and aspartate (A) are complexed in a salt form of ornithine-aspartate (OA).
3. The method of claim 1, wherein said composition comprising ornithine and a counter anion.
4. The method of claim 1, wherein said composition comprising aspartate and a counter cation.
5. The method of claim 1, wherein said composition comprises free form of ornithine and/or free form of aspartate.
6. The method of claim 1, wherein said composition comprises ornithine and/or aspartate in its pharmaceutically accepted salt form.
7. The method of claim 1, wherein the amount of ornithine and/or aspartate administered is about 0.01 g to 20g daily.
8. The method of claim 1, wherein the amount of ornithine and/or aspartate administered is at least 0.5g, 1g or 3g daily.
9. The method of claim 1, wherein said composition comprises at least 3g ornithine-aspartate (OA) administered daily.
10. The method of claim 1, wherein said subject in need thereof suffers from diabetes.
11. The method of claim 1, further comprising administering an amount of an anti- hyperglycemic agent to said subject.
12. The method of claim 11, wherein the anti-hyperglycemic agent is selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, glinides, DPP-IV inhibitor, insulin and insulin analogues.
13. The method of claim 12, wherein the anti-hyperglycemic agent is Metformin or Sitagliptin.
14. The method of claim 11, wherein said amount of the anti-hyperglycemic agent administered is a sub-therapeutic amount.

15. The method of claim 1, wherein the composition is administered orally.
16. The method of claim 1, wherein the composition is administered by intravenous injection, inhalation, nasal insufflation, intra-arterial injection, subcutaneous administration, mucosal administration, or pharyngeal administration.
17. The method of claim 1, wherein the composition is administered for at least about 2 weeks.
18. The method of claim 1, wherein the composition is administered for at least about 1 month.
19. The method of claim 1, wherein the composition administered is contained in a foodstuff.
20. The method of claim 1, wherein the composition administered is contained in a pharmaceutical composition.
21. The method of claim 1, wherein said administering decreases the fasting serum glucose level of the subject.
22. The method of claim 1, wherein said administering decreases the serum glucose level in the subject during a glucose tolerance test.
23. The method of claim 1, wherein said subject exhibits a serum glucose level of higher than about 125 mg/dL after fasting for about 8 to 12 hours prior to said administering.
24. A method of administering an anti- hyperglycemic agent to a subject in need thereof comprising administering an amount of the anti- hyperglycemic agent in conjunction with an effective amount of a composition comprising ornithine and/or aspartate, wherein the anti-hyperglycemic agent and the composition comprising ornithine and/or aspartate synergistically lower the serum glucose level in said subject.
25. The method of claim 24, wherein said composition is administered orally.
26. The method of claim 24, wherein said composition is administered prior to, subsequent to, or concurrent with administering the anti- hyperglycemic agent.
27. The method of claim 24, wherein said composition comprises ornithine-aspartate (OA) and is administered daily.
28. The method of claim 27, the amount of ornithine-aspartate (OA) administered is about 0.01 g to 20 g daily.
29. The method of claim 24, the amount of ornithine and/or aspartate administered is at least 3 g daily.
30. The method of claim 24, wherein said amount of the anti-hyperglycemic agent is a sub-therapeutic amount.
31. The method of claim 30, wherein a side-effect of the anti-hyperglycemic agent is reduced.

32. The method of claim 24, wherein said anti-hyperglycemic agent is selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, meglitinides, glinides, α -glucosidase inhibitors, repaglinide, nateglinide, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin or insulin and insulin analogues, and any combination thereof.
33. The method of claim 24, wherein said anti-hyperglycemic agent is Metformin or Sitagliptin.
34. The method of claim 24, wherein said composition and the anti-hyperglycemic agent are administered as a single unit dose.
35. The method of claim 34, wherein said unit dosage is in a form of a tablet, a capsule, a pill, a granule, an emulsion, a gel, a plurality of beads encapsulated in a capsule, a powder, a suspension, a liquid, a semi-liquid, a semi-solid, a syrup, a slurry or a chewable.
36. A method of lowering a side-effect of an anti-hyperglycemic agent in a subject in need thereof, comprising administering to the subject an effective amount of a composition comprising ornithine and/or aspartate in conjunction with a sub-therapeutic amount of an anti-hyperglycemic agent, thereby reducing a side-effect of the anti-hyperglycemic agent in said subject.
37. The method of claim 36, wherein said composition comprises ornithine-aspartate (OA) and is administered orally.
38. The method of claim 37, wherein said composition is administered daily.
39. The method of claim 37, the amount of ornithine-aspartate (OA) administered is about 0.01 g to 20 g daily.
40. The method of claim 36, the amount of ornithine and/or aspartate administered is at least 3 g daily.
41. The method of claim 36, wherein said anti-hyperglycemic agent is selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, meglitinides, glinides, α -glucosidase inhibitors, repaglinide, nateglinide, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin or insulin and insulin analogues, and any combination thereof.
42. The method of claim 36, wherein said anti-hyperglycemic agent is Metformin or Sitagliptin.
43. The method of claim 36, wherein the composition comprising ornithine and/or aspartate is in an amount effective in lowering serum glucose level in said subject administered.
44. The method of claim 36, wherein the composition comprising ornithine and/or aspartate and the anti-hyperglycemic agent synergistically lower the serum glucose level in said subject administered.
45. A composition comprising:
- (a) a sub-therapeutic amount of an anti-hyperglycemic agent; and
 - (b) an effective amount of ornithine and/or aspartate,

wherein the composition is capable of synergistically reducing the serum glucose level in a subject administered said composition as compared to administering to the subject component (a) or component (b) alone.

46. The composition of claim 45, wherein said composition is formulated in a unit dosage form.
47. The composition of claim 45, wherein said composition is formulated in a solid or liquid form.
48. The composition of claim 47, wherein said solid or liquid dosage form is a tablet, a capsule, a pill, a granule, an emulsion, a gel, a plurality of beads encapsulated in a capsule, a powder, a suspension, a liquid, a semi-liquid, a semi-solid, a syrup, a slurry or a chewable form.
49. The composition of claim 45, wherein said composition is formulated for oral consumption, intravenous injection, inhalation, nasal insufflation, intraarterial injection, subcutaneous administration, mucosal administration, or pharyngeal administration.
50. The composition of claim 45, wherein said composition is formulated for oral consumption.
51. The composition of claim 45, wherein component (a) and component (b) are separately packaged.
52. The composition of claim 45, wherein component (a) and component (b) are mixed.
53. The composition of claim 45, wherein said anti-hyperglycemic agent is selected from the group consisting of: biguanides, sulfonylureas, thiazolidinediones, meglitinides, glinides, α -glucosidase inhibitors, repaglinide, nateglinide, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin or insulin and insulin analogues, and any combination thereof.
54. The composition of claim 45, wherein said anti-hyperglycemic agent is Metformin or Sitagliptin.
55. The composition of claim 45, wherein said composition comprising ornithine-aspartate (OA) in an amount effective in lowering serum glucose level in a subject in need thereof.
56. The composition of claim 55, wherein the composition comprises about 0.01 to 20 g of ornithine-aspartate (OA).
57. The composition of claim 45, wherein the composition comprises at least about 1 g of ornithine and/or aspartate.
58. The composition of claim 55, wherein the composition comprises at least about 3 g of ornithine and/or aspartate.
59. The composition of claim 45, wherein the composition is formulated for a daily dosage form.
60. The composition of claim 45, wherein the composition is capable in lowering a side effect of the anti-hyperglycemic agent as compared to administering to the subject a therapeutic amount of the anti-hyperglycemic agent alone.

Figure 1

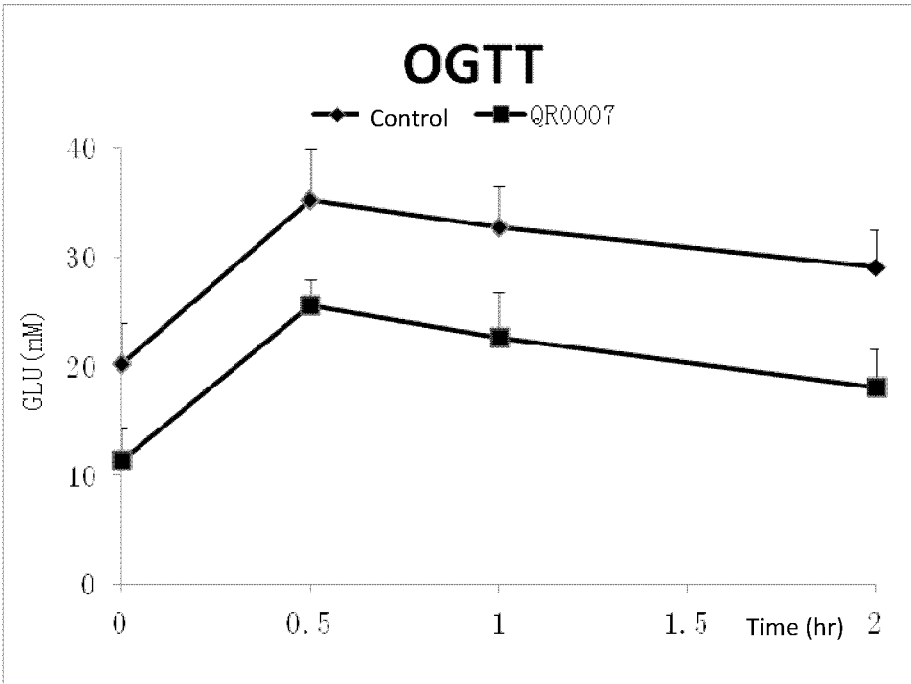


Figure 2

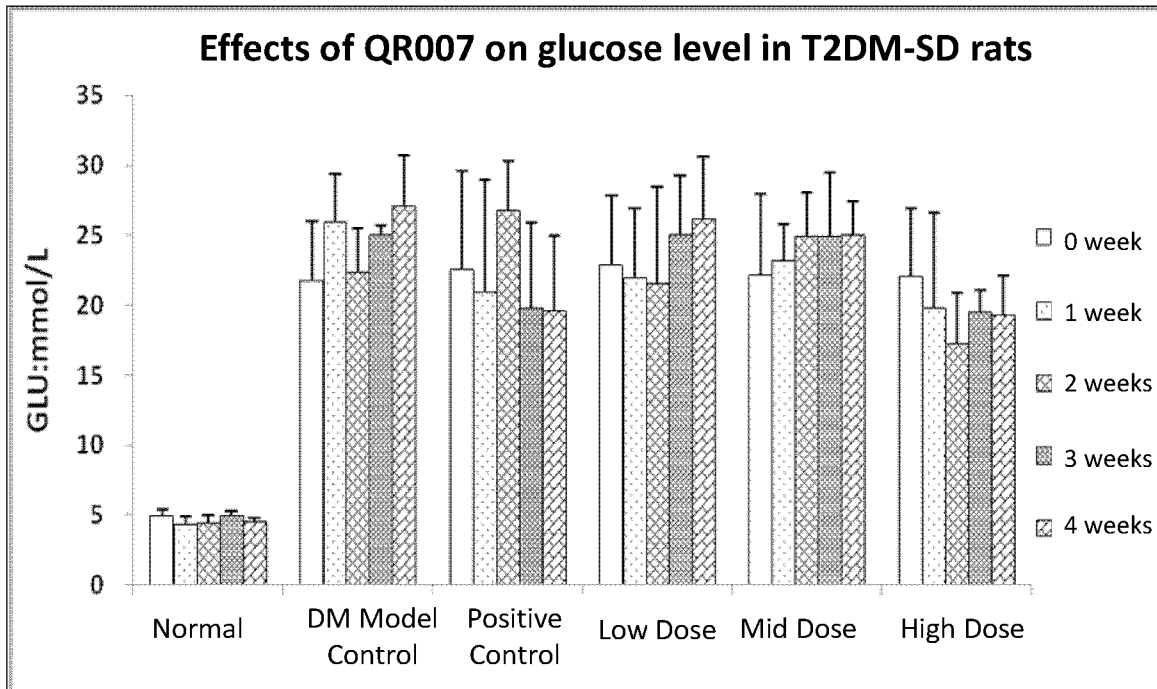
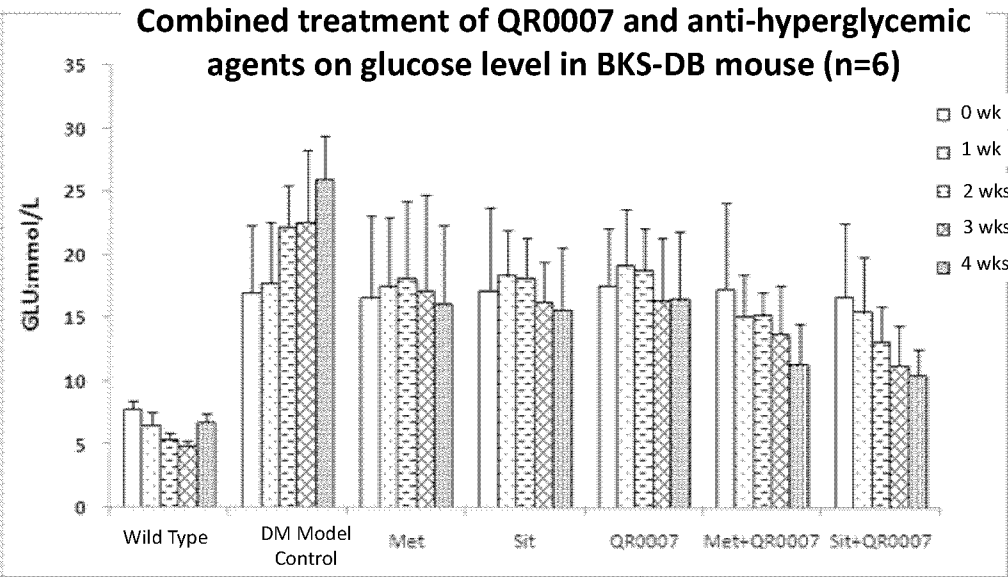


Figure 3



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2014/075963

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/198(2006.01)i; A61K 31/155(2006.01)i; A61P 3/10(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K31/-; A61P3/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, WPI, EPODOC, CNKI:hyperglycemic,hyperglycaemia, ornithine,aspartate,amino acid,synergistical,side effect, metformin,sitagliptin,nateglinide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/002365 A2 (ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY ET AL.) 04 January 2007 (2007-01-04) see page 6 lines 33-35, page 7 lines 4-6, page 14 lines 23-28, page 22 lines 15-18, page 23 lines 7-10, page 32 lines 24-30	1-35, 45-60
Y	WO 2007/002365 A2 (ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY ET AL.) 04 January 2007 (2007-01-04) see page 6 lines 33-35, page 7 lines 4-6, page 14 lines 23-28, page 22 lines 15-18, page 23 lines 7-10, page 32 lines 24-30	36-44
Y	US 2006/0205633 A1 (AJINOMOTO CO. INC.) 14 September 2006 (2006-09-14) see paragraphs [0011], [0017], [0020], [0027]	36-44
Y	US 2006/0159746 A1 (TROUP JOHN P ET AL.) 20 July 2006 (2006-07-20) see paragraphs [0005], [0016], [0058]	36-44
Y	US 2007/0004623 A1 (INNODIA INC.) 04 January 2007 (2007-01-04) see paragraphs [0005], [0006]	36-44



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

05 January 2015

Date of mailing of the international search report

02 February 2015

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2014/075963

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 101926853 A (ZHEJIANG JINGXIN PHARM. CO. LTD.) 29 December 2010 (2010-12-29) see paragraphs [0006], [0030]	1-60

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2014/075963

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **1-44**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 1-44 direct to methods for treatment of the human or animal body by therapy, and they do not meet the criteria set out in PCT Rules 39.1 (iv). The statement has been carried out and based on the use of the composition for the manufacturing of a medicament for the treatment of diseases.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2014/075963

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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				US	2013209433	A1	15 August 2013
				WO	2007002365	A3	25 October 2007
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				SG	115110	B	31 October 2007
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				ZA	200604094	A	26 September 2007
				EP	1701735	A2	20 September 2006
				JP	2008500955	A	17 January 2008
				CN	1921881	A	28 February 2007
				BR	PI0415781	A	26 December 2006
				WO	2005039626	A3	16 June 2005
				MX	2006004698	A	01 July 2006
				IN	200602881	P1	03 August 2007
				AU	2004282999	A1	15 June 2006
CN	101926853	A	29 December 2010	CN	101926853	B	14 August 2013