

Use of *Lacticaseibacillus paracasei* Lc19 for reducing blood glucose**PRIORITY**

[0001] The application claims the priority to and the benefit of Chinese Patent Application No. 202410620689.1, filed on May 17, 2024 and entitled “Use of *Lacticaseibacillus paracasei* Lc19 for reducing blood glucose”, the contents of which are incorporated herein by reference in entirety.

TECHNICAL FIELD

[0002] The disclosure relates to the field of microbiology. In particular, the disclosure relates to the use of *Lacticaseibacillus paracasei* Lc19, the composition comprising the same and related postbiotics for the treatment and prevention of a metabolic-related disease.

BACKGROUND

[0003] Probiotics have undergone years of development and exploration from their inception to clinical application. The categories and mechanisms of action of probiotics have become increasingly clear, and clinical applications have become more widespread, involving organ protection, immunity, antibacterial activity, blood lipid reduction, blood glucose reduction, weight control, etc. In China, various probiotic preparations have shown good prospects for preventing or treating diseases, but most of the current studies are small-scale. The molecular mechanism on how these probiotics work and the target acted on by the probiotics are not clear.

[0004] *Lacticaseibacillus paracasei* (*L. paracasei*) Lc19 was first disclosed in the Chinese patent application CN 202010507598.9. In this Chinese patent application, it was previously named *L. paracasei* Lc19. It not only has significant therapeutic effects on constipation and colitis, but also can improve various gut microbiota characteristic of constipation and colitis targetedly, increasing the

abundance of various beneficial bacteria and reducing the abundance of various harmful bacteria, maintaining the balance of gut microbiota, and greatly improving the ability to restore the health and diversity of gut microbiota. A strain of *L. paracasei* Lc19 has been deposited with the China General Microbiological Culture Collection Center, with Deposit NO. CGMCC NO. 17827.

[0005] Chinese patent application CN202010506279.6 discloses a yogurt comprising *L. paracasei* Lc19, a preparation method and use thereof. The yogurt not only exhibits significant therapeutic effects on constipation and colitis but also can improve various gut microbiota characteristic of constipation and colitis targetedly, increasing the abundance of various beneficial bacteria and reducing the abundance of various harmful bacteria, maintaining the balance of gut microbiota. The yogurt fundamentally restores the health and diversity of gut microbiota. It has the advantages of convenient consumption, simple treatment, a high remission rate, and no toxic side effects.

[0006] Chinese patent application CN202010635622.7 discloses a lactic acid bacteria composition comprising *L. paracasei* Lc19, which has the effect of regulating intestinal flora characteristic of the constipation.

[0007] Chinese patent application CN202111566851.9 discloses a room temperature yogurt comprising xylo-oligosaccharides and inactivated *L. paracasei* Lc19, which can improve the stability of yogurt at room temperature and reduce water separation.

[0008] There is still a need in the prior art to further expand the application of *L. paracasei*.

SUMMARY

[0009] The present inventors discovered that *L. paracasei* can produce a cholic acid conjugated to tryptophan (TrpCA or TRP-CA) in vivo or in vitro in the course of studying *L. paracasei*. Surprisingly, the inventors have found that the

cholic acid conjugated to tryptophan can promote the secretion of GLP-1 and insulin, improve glucose tolerance, and reduce the levels of serum AST and ALT, which are key indicators of liver function.

[0010] In an aspect, provided herein is the use of *L. paracasei* or postbiotics thereof for the manufacture of a pharmaceutical composition or food composition for generating a cholic acid conjugated to tryptophan.

[0011] In an embodiment, the pharmaceutical composition is used for preventing and/or treating a metabolic disease or for promoting GLP-1 and/or insulin production.

[0012] In an embodiment, the food composition is used for maintaining healthy blood glucose level, maintaining a healthy blood lipid and/or controlling body fat.

[0013] In an aspect, provided herein is a method for preventing and/or treating a metabolic disease in a subject, comprising administering to the subject *L. paracasei* or postbiotics thereof, or a pharmaceutical composition comprising the *L. paracasei* or the postbiotics thereof. In another aspect, provided herein is a method for promoting the production of GLP-1 and/or insulin, comprising administering to a subject *L. paracasei* or postbiotics thereof, or a pharmaceutical composition comprising the *L. paracasei* or the postbiotics thereof.

[0014] In yet another aspect, provided herein is a method for maintaining healthy blood glucose level, maintaining healthy blood lipid and/or controlling body fat in a subject, comprising administering to the subject *L. paracasei* or postbiotics thereof, or a pharmaceutical composition comprising the *L. paracasei* or the postbiotics thereof.

[0015] In an embodiment of the above aspects, the *L. paracasei* is deposited with the Accession Number CGMCC NO. 17827.

[0016] In an embodiment of the above aspects, *L. paracasei* is in a form of a powder or a culture solution.

[0017] In an embodiment of the above aspects, the metabolic disease is a GLP-1 related metabolic disease.

[0018] In an embodiment of the above aspects, the metabolic disease is selected from a group consisting of diabetes or a disease associated with diabetes.

[0019] In an embodiment of the above aspects, the diabetes is selected from a group consisting of type 1 diabetes, type 2 diabetes, gestational diabetes, obesity diabetes, autoimmune diabetes and borderline diabetes.

[0020] In an embodiment of the above aspects,, the disease associated with diabetes is selected from a group consisting of obesity, an obesity-related disorder, metabolic syndrome, diabetic neuropathy, a kidney disease such as diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, diabetic gangrene, xerostomia, hypoacusis, diabetic cachexia, delayed wound healing, diabetic dyslipidemia, a peripheral blood circulation disorder, non-alcoholic steatohepatitis, pre-diabetes, hyperlipemia, a fatty liver disease, impaired fasting glucose, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, elevated blood fatty acid or glycerol levels, impaired wound healing, glucose intolerance, increased fasting glucose and dyslipidemia, pancreatic beta cell insufficiency, enteroendocrine cell insufficiency, glycosuria, metabolic acidosis, cataract, a diabetic coronary heart disease, a diabetic cerebrovascular disease, a diabetic peripheral vascular disease, metabolic syndrome, atherosclerosis and stroke.

[0021] In an embodiment of the above aspects, the obesity is selected from a group consisting of symptomatic obesity, simple obesity, childhood obesity, morbid obesity and abdominal obesity.

[0022] In an embodiment of the above aspects, a disease associated with obesity is selected from a group consisting of glucose tolerance, abnormal lipid metabolism, hyperlipidemia, hypertension, heart failure, hyperuricemia, gout,

fatty liver, a coronary heart disease, cerebral infarction, sleep apnea syndrome, obesity hypoventilation syndrome and visceral obesity syndrome.

[0023] In an embodiment of the above aspects, the pharmaceutical or food composition is further used for ameliorating constipation and/or ameliorating inflammatory bowel disease.

[0024] In an embodiment of the above aspects, the constipation is functional constipation and the inflammatory bowel disease is colitis or Crohn's disease.

[0025] In an embodiment of the above aspects, the pharmaceutical composition further comprises probiotics, prebiotics and/or a pharmaceutically acceptable carrier, diluent or excipient.

[0026] In an embodiment of the above aspects, the food composition further comprises probiotics, prebiotics and/or a food-acceptable carrier, diluent or excipient.

[0027] In an embodiment of the above aspects, the pharmaceutical composition is an oral composition, preferably selected a group consisting of an enteric coated tablet, a granule, a capsule, a tablet, a powder, an oral liquid, a suspension and an emulsion.

[0028] In an embodiment of the above aspects, the food composition is a liquid, semi-solid or solid, preferably selected from the group consisting of a dairy product, a confectionery product, a fruit juice and an instant food product.

[0029] In an embodiment of the above aspects, a unit dose of the pharmaceutical or food composition comprises 1×10^4 - 1×10^{12} cfu/mL, 1×10^4 - 1×10^9 cfu/mL or 1×10^5 - 1×10^8 cfu/mL viable bacteria.

[0030] In another aspect, provided herein is a composition comprising *L. paracasei* for use in generating a cholic acid conjugated to tryptophan, which is a pharmaceutical composition for preventing and/or treating a metabolic disease or for promoting GLP-1 and/or insulin production, or a food composition for maintaining healthy blood glucose level, maintaining healthy blood lipid and/or

controlling body fat. In an embodiment, the pharmaceutical composition further comprises another active ingredient for preventing and/or treating a metabolic disease, or the food composition further comprises another food active ingredient for maintaining healthy blood glucose level, maintaining healthy blood lipid and/or controlling body fat.

[0031] In an embodiment of the above aspects, the *L. paracasei* is deposited with the Accession Number CGMCC NO. 17827.

[0032] In an embodiment of the above aspects, the other active ingredient is one or more of a biguanide, a sulfonylurea, a glinide, an alpha-glucosidase inhibitor, a thiazolidinedione and a GLP-1 drug.

[0033] In an embodiment of the above aspects, the pharmaceutical composition is an oral composition, preferably selected from the group consisting of an enteric coated tablet, a granule, a capsule, a tablet, a powder, an oral liquid, a suspension and an emulsion.

[0034] In an embodiment of the above aspects, the pharmaceutical composition further comprises probiotics, prebiotics and/or a pharmaceutically acceptable carrier, diluent or excipient.

[0035] In an embodiment of the above aspects, the food composition is a liquid, semi-solid or solid, preferably selected from a group consisting of a dairy product, a confectionery product, a fruit juice and an instant food product.

[0036] In an embodiment of the above aspects, the food composition further comprises probiotics, prebiotics and/or a food-acceptable carrier, diluent or excipient.

[0037] In another aspect, provided herein is a method for producing a cholic acid conjugated to tryptophan, comprising culturing *L. paracasei* in a medium in the presence of a bile acid and tryptophan to produce the cholic acid conjugated to tryptophan.

[0038] In an embodiment of the above aspects, the *L. paracasei* is *L. paracasei*

deposited with the Accession Number CGMCC NO. 17827.

[0039] In another aspect, provided herein is use of *L. paracasei* for the production of a cholic acid conjugated to tryptophan. In an embodiment, the *L. paracasei* is *L. paracasei* deposited with the Accession Number CGMCC NO. 17827.

[0040] In another aspect, provided herein is a method for screening a strain of the genus *Lactobacillus* that produces a cholic acid conjugated to tryptophan, comprising:

[0041] (1) culturing a strain of the genus *Lactobacillus* in a medium in the presence of a bile acid and tryptophan to obtain a culture supernatant;

[0042] (2) measuring the content of cholic acid conjugated to tryptophan in the culture supernatant; and

[0043] (3) selecting the strain of the genus *Lactobacillus* that produces cholic acid conjugated to tryptophan.

[0044] In an embodiment, the method is a method for screening a strain of the genus *Lactobacillus* that promotes GLP-1 and/or insulin production.

[0045] In an embodiment, the strain of the genus *Lactobacillus* is *L. paracasei*, preferably the *L. paracasei* which is deposited with Accession NO. CGMCC NO. 17827.

[0046] In another aspect, the present disclosure provides *L. paracasei* or postbiotics thereof or composition comprising the *L. paracasei* or postbiotics thereof for use in generating a cholic acid conjugated to tryptophan.

[0047] In another aspect, the present disclosure provides *L. paracasei* or postbiotics thereof or composition comprising the *L. paracasei* or postbiotics thereof for use in preventing and/or treating a metabolic disease or for promoting GLP-1 and/or insulin production, and/or for use in maintaining healthy blood glucose level, maintaining healthy blood lipid and/or controlling body fat.

[0048] In an embodiment, the *L. paracasei* is deposited with the Accession Number CGMCC NO. 17827. In an embodiment, the *L. paracasei* is in a form of a powder or a culture solution.

[0049] In an embodiment, the metabolic disease is a GLP-1 related metabolic disease, optionally selected from a group consisting of diabetes or a disease associated with diabetes such as those defined herein.

[0050] In an embodiment, the *L. paracasei* or postbiotics thereof or composition comprising the *L. paracasei* or postbiotics thereof is further for use in ameliorating constipation and/or ameliorating inflammatory bowel disease. In an embodiment, the constipation is functional constipation and the inflammatory bowel disease is colitis or Crohn's disease. In an embodiment, the *L. paracasei* or postbiotics thereof is administrated at 1×10^4 - 1×10^{12} cfu/mL, 1×10^4 - 1×10^9 cfu/mL or 1×10^5 - 1×10^8 cfu/mL viable bacteria. In an embodiment, the *L. paracasei* or postbiotics thereof is administrated orally. In an embodiment, the composition is a pharmaceutical composition or a food composition. In an embodiment, the pharmaceutical composition further comprises probiotics, prebiotics and/or a pharmaceutically acceptable carrier, diluent or excipient. In an embodiment, the food composition further comprises probiotics, prebiotics and/or a food-acceptable carrier, diluent or excipient. In an embodiment, the pharmaceutical composition is an oral composition, preferably selected from a group consisting of an enteric coated tablet, a granule, a capsule, a tablet, a powder, an oral liquid, a suspension and an emulsion. In an embodiment, the food composition is a liquid, semi-solid or solid, preferably selected from a group consisting of a dairy product, a confectionery product, a fruit juice and an instant food product. In an embodiment, a unit dose of the pharmaceutical or food composition comprises 1×10^4 - 1×10^{12} cfu/mL, 1×10^4 - 1×10^9 cfu/mL or 1×10^5 - 1×10^8 cfu/mL viable bacteria.

[0051] In another aspect, the present disclosure provides a composition comprising *L. paracasei* wherein the composition is a pharmaceutical

composition or a food composition, the pharmaceutical composition further comprises another active ingredient for preventing and/or treating a metabolic disease, or the food composition further comprises another food active ingredient for maintaining healthy blood glucose level, maintaining healthy blood lipid and/or controlling body fat. In an embodiment, the *L. paracasei* is deposited with the Accession Number CGMCC NO. 17827. In an embodiment, the another active ingredient is one or more of a biguanide, a sulfonylurea, a glinide, an alpha-glucosidase inhibitor, a thiazolidinedione and a GLP-1 drug. In an embodiment, the pharmaceutical composition is an oral composition, preferably selected from a group consisting of an enteric coated tablet, a granule, a capsule, a tablet, a powder, an oral liquid, a suspension and an emulsion. In an embodiment, the pharmaceutical composition further comprises probiotics, prebiotics and/or a pharmaceutically acceptable carrier, diluent or excipient. In an embodiment, the food composition is a liquid, semi-solid or solid, preferably selected from a group consisting of a dairy product, a confectionery product, a fruit juice and an instant food product. In an embodiment, the food composition further comprises probiotics, prebiotics and/or a food-acceptable carrier, diluent or excipient.

[0052] Advantages of the present disclosure include:

[0053] 1. The inventors discover for the first time that *L. paracasei* can generate a cholic acid conjugated to tryptophan, and the cholic acid conjugated to tryptophan can significantly promote the secretion of GLP-1 in an animal model *in vivo* and in a cell model *in vitro*, thereby reducing weight, reducing blood sugar, and relieving symptoms of non-alcoholic fatty liver disease.

[0054] 2. The inventors have found that colonization of *L. paracasei* can also have effects such as improvement of blood sugar metabolism.

DESCRIPTION OF THE DRAWINGS

[0055] Fig. 1 shows the structural formula of the cholic acid conjugated to

tryptophan.

[0056] Fig. 2 shows the effect of the cholic acid conjugated to tryptophan on body weight of mice fed with a high-fat diet. The statistical method was a two-way ANOVA on duplicate measurements with unpaired T test. * $P < 0.05$, ** $P < 0.01$.

[0057] Fig. 3 shows the effect of the cholic acid conjugated to tryptophan on glucose tolerance of mice fed with a high-fat diet. The upper panel of Fig. 3 shows the change in blood glucose level over time. The lower panel of Fig. 3 shows the AOC (area of the curve) of the control and treated groups. The statistical method was two-way ANOVA on duplicate measurements with unpaired T test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[0058] Fig. 4 shows the effect of the cholic acid conjugated to tryptophan on serum AST and ALT of mice fed with a high-fat diet. The statistical method was a two-tailed unpaired T test. * $P < 0.05$, *** $P < 0.001$.

[0059] Fig. 5 shows the effect of *L. paracasei* Lc19 on glucose tolerance of mice fed with a high-fat diet. The statistical method was two-way ANOVA on duplicate measurements with unpaired T test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. The upper panel of Fig. 5 shows the change in blood glucose level over time. The lower panel of Fig. 5 shows the AOC (area of the curve) of the control and treated groups.

DETAILED DESCRIPTION

[0060] Metabolic disease is a general term for diseases that occur due to metabolic disorders in the body. Metabolic diseases are usually caused by an imbalance of carbohydrates, lipids, proteins, vitamins, electrolytes, water, etc. Examples of metabolic diseases include obesity, diabetes, hyperlipidemia, arteriosclerosis, hypertension, non-alcoholic fatty liver disease, and the like. With the development of society, the continuous improvement of people's living standards and the adjustment of dietary structure, the trend of dietary surplus has

led to the increasing incidence of metabolic diseases, among which obesity, hyperglycemia and hyperlipidemia are the most attractive. Obesity is an inducer of a range of diseases, such as hypertension, diabetes, coronary heart disease, gallbladder disease, osteoarthritis, and respiratory distress during sleep. In addition, the incidence of cardiovascular diseases such as atherosclerosis and coronary heart disease caused by elevated blood lipids is increasing year by year, and there is a trend that the diseases occur in younger patients. Weight loss, hypoglycemic drugs and hypolipidemic drugs have become one of the focuses of drug research.

[0061] Cholic acid conjugated to tryptophan is a newly discovered amino acid-conjugated cholic acid produced by bacteria in recent years, which is ubiquitous in human beings, but its physiological function has not been reported. The research results of the inventors show that the cholic acid conjugated to tryptophan can significantly promote the secretion of GLP-1 in an animal model *in vivo* and in a cell model *in vitro*, and play a role in reducing weight, reducing blood sugar and relieving the symptoms of non-alcoholic fatty liver disease. The colonization of probiotics capable of generating the cholic acid conjugated to tryptophan can also play the same role in improving metabolism.

[0062] Through extensive and in-depth research and experiments, the inventors found that cholic acid conjugated to tryptophan has the function of preventing and treating metabolism-related diseases (including obesity, diabetes and fatty liver). The inventors screen out strains capable of producing cholic acid conjugated to tryptophan through *in vitro* experiments, and *L. paracasei* capable of producing cholic acid conjugated to tryptophan is used to colonize mice fed with a high-fat diet. It was found that bacterial colonization could also reduce blood sugar and effectively alleviate diabetes through the production of cholic acid conjugated to tryptophan. On this basis, the present disclosure is completed.

[0063] As used herein, the term “glucagon-like peptide-1 (GLP-1)” is a hormone mainly produced by intestinal L cells. GLP-1 plays a role in reducing

blood sugar by promoting insulin secretion, and can also reduce weight and blood lipid by suppressing appetite and promoting energy metabolism.

[0064] As used herein, the term “cholic acid conjugated to tryptophan” refers to a conjugate formed by the reaction of the amino group of tryptophan with the carboxyl group at position 24 of a bile acid to form an amide bond. The structure of cholic acid conjugated to tryptophan is shown in Fig. 1. Cholic acid conjugated to tryptophan has been reported, for example, in Nature. 2024 Feb; 626(7998):419-426. doi: 10.1038/s41586-023-06906-8. Epub 2023 Dec 5.

[0065] As used herein, the term “postbiotics” refers to genetically defined inactivated microorganisms and/or microbial components, including or not including their metabolites, that are beneficial to the health of the host, excluding chemically synthesized components and viruses/bacteriophages as well as their products (see the group standard T/CBFIA 09001-2023 of China Biotech Fermentation Industry Association). In the present application, the postbiotics of *L. paracasei* comprises cholic acid conjugated to tryptophan.

[0066] As used herein, the term “metabolic disease” generally refer to a disease or condition that disrupts the normal metabolic process in the body, making it impossible for the body to use and/or store energy normally. The metabolic disease can be any metabolic disease that benefits from modulating (e.g., increasing) GLP-1 activity, or any metabolic disease that benefits from agonizing GLP-1 receptor activity. The metabolic disease may be a GLP-1 related metabolic disease, including diabetes or a disease associated with diabetes. Diabetes includes, but is not limited to, type 1 diabetes, type 2 diabetes, gestational diabetes, obesity diabetes, autoimmune diabetes and/or borderline diabetes. The disease associated with diabetes include, but is not limited to, obesity, obesity-related disorder, metabolic syndrome, diabetic neuropathy, a kidney disease such as diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, diabetic gangrene, xerostomia, hypoacusis, diabetic cachexia, delayed

wound healing, diabetic dyslipidemia, a peripheral blood circulation disorder, non-alcoholic steatohepatitis, pre-diabetes, hyperlipemia, a fatty liver disease, impaired fasting glucose, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, elevated blood fatty acid or glycerol levels, impaired wound healing, glucose intolerance, increased fasting glucose and dyslipidemia, pancreatic beta cell insufficiency, enteroendocrine cell insufficiency, glycosuria, metabolic acidosis, cataract, a diabetic coronary heart disease, a diabetic cerebrovascular disease, a diabetic peripheral vascular disease, metabolic syndrome, atherosclerosis and/or stroke. Obesity includes, but is not limited to, symptomatic obesity, simple obesity, childhood obesity, morbid obesity and abdominal obesity. A disease associated with obesity include, but is not limited to, glucose tolerance, abnormal lipid metabolism, hyperlipidemia, hypertension, heart failure, hyperuricemia, gout, fatty liver, a coronary heart disease, cerebral infarction, sleep apnea syndrome, obesity hypoventilation syndrome and visceral obesity syndrome.

[0067] As used herein, the term “prevention” or “preventing” refers to a delay in the onset of, and/or a reduction in the frequency and/or severity of, one or more symptoms of a particular disease, disorder, or condition. The term “treatment” or “treating” refers to any administration of a therapy that partially or completely alleviates, ameliorates, mitigates, inhibits one or more symptoms, features and/or causes of a particular disease, condition and/or disorder, delays its onset, reduces its severity, and/or reduces its incidence rate.

[0068] As used herein, the term “subject” refers to an individual receiving administration of the provided treatment. In some embodiments, the subject is an animal. In some embodiments, the subject is a mammal, e.g., a mammal that experiences or is susceptible to a metabolic disease as described herein. In some embodiments, the animal is a vertebrate, e.g., a mammal, such as a non-human primate (particularly a higher primate), sheep, dog, rodent (e.g., mouse or rat), guinea pig, goat, pig, cat, rabbit, or cow. In some embodiments, the subject is a

human.

[0069] As used herein, “pharmaceutically effective amount” means an amount sufficient to treat or prevent a disease at a reasonable benefit-risk ratio appropriate for medical treatment or prevention. Effective dosage level may be determined based on factors including the severity of the disease, the activity of the drug, the age, weight, health of the patient, sex of the patient, the sensitivity of the patient to the drug, the timing of administration, route of administration, and release rate of the drug, duration of treatment, drugs used in combination or concurrently with the composition, and other factor known in the medical arts. A pharmaceutical composition according to one example may be administered as the therapeutic agent alone, or in combination with other therapeutic agents, and may be administered sequentially or concurrently with conventional therapeutic agents. In addition, it may be administered singly or in multiple times. Taking all factors into consideration, it is important to administer an amount that can achieve the maximized efficacy with the minimized amount without side effects.

[0070] Treatment method

[0071] The present disclosure provides the use of *L. paracasei* or postbiotics thereof for the production of cholic acid conjugated to tryptophan. The inventors have found that cholic acid conjugated to tryptophan can be used for preventing and/or treating a metabolic disease or promoting GLP-1 and/or insulin production. Thus, the *L. paracasei* or postbiotics thereof may be used in a medicament or pharmaceutical composition for preventing and/or treating a metabolic disease or for promoting GLP-1 and/or insulin production. In addition, *L. paracasei* or postbiotics thereof may also be used in a food product or food composition for maintaining healthy blood glucose level, maintaining healthy lipid level and/or controlling body fat.

[0072] In the present disclosure, the treatment method may be a method of preventing and/or treating a metabolic disease in a subject, or may be a method for promoting GLP-1 and/or insulin production in a subject. The method may

include administering to the subject *L. paracasei* or postbiotics thereof, such as by orally administering *L. paracasei* or postbiotics thereof. In a treatment method, *L. paracasei* or postbiotics is administered at a dose and for a period of time sufficient to colonize *L. paracasei* in the intestinal tract of a subject. Pharmaceutically effective amounts and periods of administration of probiotics are known to those skilled in the art. For example, a pharmaceutically effective amount may be in a range from 10 to 10^{15} , from 10^2 to 10^{14} , from 10^3 to 10^{13} , from 10^4 to 10^{12} , from 10^5 to 10^{11} , from 10^6 to 10^{10} , from 10^2 to 10^7 , from 10^2 to 10^8 , or from 10^2 to 10^9 colony forming units (CFU).

[0073] The strain of *L. paracasei* is not particularly limited, but it is preferable that *L. paracasei* is *L. paracasei* having the Accession NO. CGMCC NO. 17827. *L. paracasei* is not particularly limited in the form, and may be in the form of a lyophilized powder or a culture solution.

[0074] The methods of the disclosure may be used for treating or preventing a metabolic disease in a subject. The metabolic disease may be a GLP-1 related metabolic disease, preferably selected from a group consisting of diabetes or a disease associated with diabetes. The diabetes may be selected from a group consisting of type 1 diabetes, type 2 diabetes, gestational diabetes, obesity diabetes, autoimmune diabetes and borderline diabetes. The disease associated with diabetes may be selected from a group consisting of obesity, an obesity-related disorder, metabolic syndrome, diabetic neuropathy, a kidney disease such as diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, diabetic gangrene, xerostomia, hypoacusis, diabetic cachexia, delayed wound healing, diabetic dyslipidemia, a peripheral blood circulation disorder, non-alcoholic steatohepatitis, pre-diabetes, hyperlipemia, a fatty liver disease, impaired fasting glucose, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, elevated blood fatty acid or glycerol levels, impaired wound healing, glucose intolerance, increased fasting glucose and

dyslipidemia, pancreatic beta cell insufficiency, enteroendocrine cell insufficiency, glycosuria, metabolic acidosis, cataract, a diabetic coronary heart disease, a diabetic cerebrovascular disease, a diabetic peripheral vascular disease, metabolic syndrome, atherosclerosis and stroke. The obesity may be selected from a group consisting of symptomatic obesity, simple obesity, childhood obesity, morbid obesity and abdominal obesity. A disease associated with obesity may be selected from a group consisting of glucose tolerance, abnormal lipid metabolism, hyperlipidemia, hypertension, heart failure, hyperuricemia, gout, fatty liver, a coronary heart disease, cerebral infarction, sleep apnea syndrome, obesity hypoventilation syndrome and visceral obesity syndrome.

[0075] The methods of the disclosure may further be used for ameliorating constipation and/or ameliorating inflammatory bowel disease. For example, constipation is functional constipation, or inflammatory bowel disease is colitis or Crohn's disease.

[0076] The methods of the present disclosure may be suitable for any mammalian subject, but are preferably suitable for human subjects. As described above, the metabolic disease to be treated by the present method is a GLP-1 related metabolic disease, preferably selected from a group consisting of diabetes or a disease associated with diabetes.

[0077] Composition

[0078] The composition administered to the subject may be a food composition such as, but not limited to, a drink, a dairy product, a solid food. The food composition may further comprise additional probiotics, prebiotics, and/or a food-acceptable carrier, diluent, or excipient. The composition administered to the subject may also be a pharmaceutical composition. The pharmaceutical composition can further comprise another active ingredient for preventing and/or treating a metabolic disease, preferably, the other active ingredient is one or more of biguanides, sulfonylureas, glinides, alpha-glucosidase inhibitors, thiazolidinediones and GLP-1 drugs. The composition herein may be an oral

composition, preferably selected from a group consisting of granules, capsules, tablets, powders, oral liquids, suspensions, and emulsions. The amount of *L. paracasei* or postbiotics thereof in the composition should be an effective amount. Those skilled in the art can conventionally determine a therapeutically or prophylactically effective amount of probiotics, such as *L. paracasei* or postbiotics thereof. For example, a unit dose of the *L. paracasei* or postbiotics thereof in the composition comprises 1×10^3 - 1×10^{12} cfu/mL, 1×10^4 - 1×10^9 cfu/mL, or 1×10^5 - 1×10^8 cfu/mL viable bacteria.

[0079] Some non-limiting examples of food products to be used together with the methods and compositions described herein include: ice-cream stick, cheese, cream, chocolate, milk, and the like. In other embodiments, the food product may be fruit juices, refreshing drinks, tea drinks, drink products, jelly drinks and functional drinks; alcoholic drinks such as beer; carbohydrate-containing foods such as rice foods, noodles, bread and cooked wheaten food; pasty products such as fish, ham, sausage, seafood pasty product; steamed bagged product such as curry, thick starch-coated food, and Chinese soup; soup; dairy products such as milk, dairy drink, ice cream, and yogurt; fermented products such as fermented soy milk, fermented drink, and pickle; bean products; various confectionery products, including biscuit, cookie, etc., candy, gum, fudge, cold dessert (including jelly, cream caramel, and frozen dessert); instant food such as instant soup and instant bean soup; and the like. In one embodiment, the food product for administration is frozen. In some embodiments, the food product may be or comprise one or more of bars, candies, baked goods, cereals, savory snacks, cooked wheaten foods, chocolates and other solid foods, as well as liquids or semi-solid foods (including yogurt, soups, and stews) and drinks (such as smoothies, shakes, juices, and other carbonated or non-carbonated drinks).

[0080] The oral composition may comprise an inert diluent or an edible carrier. For oral therapeutic administration, the active compounds may be blended with excipients and used in the form of tablets, lozenges, pastilles, troches, or capsules

(e.g., gelatin capsules). The oral composition may also be prepared by combining the composition of the present disclosure with food. In some embodiments, the probiotics may be formulated in the food product.

[0081] In some embodiments, the composition is administered to the subject in a single dose. In some embodiments, the composition is administered to the subject in multiple doses. In some embodiments, the dosage of the composition is administered to the subject twice daily, daily, weekly, or monthly.

[0082] In some embodiments, the unit dose comprises from 10 to 10^{15} , from 10^2 to 10^{14} , from 10^3 to 10^{13} , from 10^4 to 10^{12} , from 10^5 to 10^{11} , from 10^6 to 10^{10} , from 10^2 to 10^7 , from 10^2 to 10^8 , or from 10^2 to 10^9 colony forming units (CFU). In some embodiments, the probiotics may be a viable cell. In some embodiments, the composition comprises a cell culture of probiotics and/or a culture supernatant thereof and/or a powder formed therefrom, and/or the composition is formulated by using a cell culture of probiotics and/or a culture supernatant thereof and/or a powder formed therefrom.

[0083] The pharmaceutical composition is generally formulated to be compatible with their intended route of administration. Examples of routes of administration include oral administration. Methods of formulating suitable pharmaceutical compositions are known in the art, see, for example, Remington: The Science and Practice of Pharmacy, 21st Edition, 2005; and books in the Drugs and the Pharmaceutical Sciences: a Series of Textbooks and Monographs (Dekker, NY) series. The oral composition typically comprises an inert diluent or an edible carrier. For example, an oral formulation may be or comprise a syrup, liquid, tablet, lozenge, fondant, capsule (e.g., gelatin capsule), powder, gel, film, or the like.

[0084] Lactose, glucose, sucrose, sorbitol, mannose, starch, acacia, calcium phosphate, alginate, gelatin, calcium silicate, fine crystalline cellulose, polyvinylpyrrolidone (PVP), cellulose, water, syrup, methylcellulose, methylparaben, propylparaben, talc, magnesium stearate, mineral oil, or the like

may be used as a carrier, excipient, diluent, or the like for the pharmaceutical composition of the present disclosure.

[0085] In addition, the pharmaceutical composition of the present disclosure may further comprise a lubricant, a wetting agent, an emulsifier, a suspoemulsion stabilizer, a preservative, a sweetener, a flavor, and the like. The pharmaceutical composition of the present disclosure can be produced in an enteric-coated formulation by a variety of well-known methods so that the microorganisms, which are the active ingredients of the pharmaceutical composition, can smoothly pass through the stomach without being destroyed by gastric acid.

[0086] The pharmaceutical composition of the present disclosure can be made into enteric coated tablets for oral administration. The term “enteric coating” in the present application includes all conventional medicinally acceptable coatings which are not degraded by gastric acid but are sufficiently broken down in the small intestine to rapidly release the microorganisms of the present disclosure. The enteric-coating of the present disclosure can be maintained for more than 2 hours in synthetic gastric acid, such as HCl solution at pH = 1, at 36-38°C, and is preferably decomposed within 1.0 hour in synthetic intestinal fluid, such as buffer solution at pH = 7.0.

[0087] The enteric coating of the present disclosure is coated at about 16-30 mg per tablet, preferably 16-25 mg, more preferably 16-20 mg. In the present disclosure, the thickness of the enteric coating is 5-100 μm , and the ideal thickness is 20-80 μm . The component of the enteric coating may be prepared using conventional polymers known in the art.

EXAMPLES

[0088] The experimental methods used in the following examples are conventional unless otherwise specified.

[0089] Materials, reagents, etc. used in the following examples are commercially available unless otherwise specified.

[0090] Example 1. Effect of cholic acid conjugated to tryptophan on glucose tolerance-related indicators, body weight, body fat, and liver function in obesity model mice

[0091] Materials: blood glucose test paper (commercially available from Roche), blood glucose meter (commercially available from Roche), active GLP-1 detection kit (commercially available from Merck), insulin detection kit (commercially available from CUSABIO), serum aspartate aminotransferase AST assay kit (commercially available from BioSino), serum alanine aminotransferase ALT assay kit (commercially available from BioSino).

[0092] Establishment of the mouse model: C57BL/6 mice were purchased from GemPharmatech, maintained at a temperature of 20-24°C, with a constant humidity of 50-60%, and exposed to light for 12 hours from 8:00 to 20:00 with soundproofing and with ad libitum feeding and drinking water. The mice were acclimated for one week before the experiment. C57BL/6 mice were fed with a high-fat diet for 8 weeks by gavage at a dose of 10 mg/kg body weight and a frequency of three times per week. A mouse obesity model induced by a high-fat diet in mice was established.

[0093] Methods: C57 male mice, aged 6-8 weeks, were fed with a high-fat diet and weighed 20-22g. The mice were divided into the following groups according to their body weight: (1) control group: saline containing 1% DMSO, without cholic acid conjugated to tryptophan; (2) cholic acid conjugated to tryptophan treatment group (experimental group): 6 mice in each group received 10 mg/kg of the drug three times a week for 8 weeks.

[0094] The same amount of saline was given to both groups. The two groups of mice were fed with a high-fat diet for 8 weeks, and the body weight was monitored every week. Glucose tolerance test was carried out at the second week of treatment. That is, the mice received glucose by gavage, and the GLP-1 and insulin levels of mice were detected at different time points. In Table 2, GLP-1 and insulin secretion levels were measured at 0 min (i.e., before glucose

administration) and at 15 min (i.e., 15 min after glucose administration). Blood glucose of the mice was measured using a blood glucose meter at 0, 15, 30, 60, 90, and 120 minutes. GLP-1 and insulin secretion levels were detected with active GLP-1 detection kit (Merck) and insulin detection kit (CUSABIO) according to the instructions of the kits. After the last administration (week 8), body fat was detected by nuclear magnetic resonance to determine fat content and muscle content. Blood was taken and centrifuged at 3000 rpm at 4°C. Serum aspartate aminotransferase (also known as glutamic oxalacetic transaminase) AST assay kit (BioSino) and serum glutamic-pyruvic transaminase (*viz* alanine aminotransferase) ALT assay kit (BioSin) were used to determine serum ALT and AST according to the instructions of the kit.

[0095] Results: Compared with the control group, the cholic acid conjugated to tryptophan treatment group had a trend of change from the first week, and there was a significant difference in the sixth week. These results indicated that cholic acid conjugated to tryptophan had a significant impact on body weight control and could significantly reduce body fat; and can also improve glucose tolerance induced by a high-fat diet. The improvement of glucose tolerance is due to the promotion of the secretion of glucose-stimulated GLP-1 and insulin. The cholic acid conjugated to tryptophan reduced the levels of serum AST and ALT, which are key indexes of liver function. The results are shown in Figs. 2-5 and Tables 1-5. Fig. 2 shows the effect of cholic acid conjugated to tryptophan on body weight of mice fed with a high-fat diet. The statistical method was a two-way ANOVA on duplicate measurements with unpaired T test. * $P < 0.05$, ** $P < 0.01$.

[0096] Fig. 3 shows the effect of cholic acid conjugated to tryptophan on glucose tolerance of mice fed with a high-fat diet. The upper panel of Fig. 3 shows the change in blood glucose level over time. The lower panel of Fig. 3 shows the AOC (area of the curve) of the control and treated groups. The statistical method was a two-way ANOVA on duplicate measurements with unpaired T test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[0097] Fig. 4 shows the effect of cholic acid conjugated to tryptophan on serum AST and ALT of mice fed with a high-fat diet. The statistical method was a two-tailed unpaired T test. *P<0.05, ***P<0.001.

[0098] Fig. 5 shows the effect of *L. paracasei* Lc19 on glucose tolerance of mice fed with a high-fat diet. The statistical method was a two-way ANOVA on duplicate measurements with unpaired T test. *P<0.05, **P<0.01, ***P<0.001. The upper panel of Fig. 5 shows the change in blood glucose level over time. The lower panel of Fig. 5 shows the AOC (area of the curve) of the control and treated groups.

[0099] Table 1 Effect of cholic acid conjugated to tryptophan on body fat in mice fed with a high fat diet after 8 weeks of continuous administration (The statistical method is a two-tailed unpaired T test.)

Grouping	Fat content (g)	Muscle content (g)
Control group	10.1	19.3
Experimental group	5.5	19.5
P value	0.001	0.800

[0100] Table 2 Effect of cholic acid conjugated to tryptophan on body weight of mice fed with a high-fat diet (The statistical method was a two-way ANOVA on duplicate measurements with unpaired T test.)

Grouping	Body weight (g)								
	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Control group	21.2	23.4	24.7	27.3	28.6	31	33.4	34.4	37.9
Experimental group	20.7	21.6	23.3	25.4	26.5	27.5	28.6	28.8	29.2
P value	0.259	0.050	0.104	0.140	0.147	0.050	0.020	0.014	0.005

[0101] Table 3 Effect of cholic acid conjugated to tryptophan on glucose tolerance in mice fed with a high-fat diet after two weeks of continuous administration (The statistical method was a two-way ANOVA on duplicate measurements with unpaired T test.)

Grouping	Blood glucose (mg/dL)						
	0 minutes	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes	Curve area
Control group	163.2	317.7	413.1	289.5	199.1	174.6	14780.3
Experimental group	153.6	292.5	366	260.7	175.2	159.6	10813.5
P value	0.299	0.109	0.052	0.018	< 0.001	0.008	0.010

[0102] Table 4 Effects of cholic acid conjugated to tryptophan on glucose-stimulated GLP-1 and insulin in mice fed with a high-fat diet after two weeks of continuous administration (The statistical method was a two-way ANOVA on duplicate measurements with unpaired T test.)

Grouping	GLP-1 (pM)		Insulin, ng/mL	
	0 minutes	15 minutes	0 minutes	15 minutes
Control group	4.45	11.58	0.49	1.49
Experimental group	5.8	18.73	0.50	1.91
P value	0.129	< 0.001	0.951	< 0.001

[0103] Table 5 Effect of cholic acid conjugated to tryptophan on serum AST and ALT in mice fed with a high-fat diet (The statistical method is a two-tailed unpaired T test.)

Grouping	AST (U/L)	ALT (U/L)
Control group	220.80	109.44
Experimental group	155.25	66.79
P value	0.001	0.011

Example 2. Effect of Cholic acid conjugated to tryptophan on GLP-1 secreted by an intestinal L cell line GLUTag

[0104] Materials: Mouse L cells (GLUTag cells from D. J. Drucker laboratory), cultured in high-glucose medium, and active GLP-1 detection kit (from Merck).

[0105] Methods: L cells were cultured in high-glucose DMEM containing 10% fetal bovine serum to 80% cell density.

Then, 50 mM cholic acid conjugated to tryptophan was diluted to obtain cholic acid conjugated to tryptophan sample group with different final concentrations (0, 1, 10 or 50 μM). 1% DMSO solvent is used as a control. The different concentrations of cholic acid conjugated to tryptophan were added to Mouse L cell samples, which were incubated for one hour, and the supernatant was isolated to detect the level of GLP-1 in the supernatant using an active GLP-1 detection kit (Merck).

[0106] Results: Compared with the control group, cholic acid conjugated to tryptophan increased the level of GLP-1 in the cell supernatant in a dose-dependent manner. The effect of promoting the GLP-1 level is obvious at a concentration of 10 μM (Table 6).

[0107] Table 6 Effect of cholic acid conjugated to tryptophan on GLP-1 secreted by intestinal L cell line GLUTag (The statistical method was a one-way analysis of variance with Tukey's post-test)

Grouping	Concentration of cholic acid conjugated to tryptophan (μM)			
	0	1	10	50
GLP-1 content (pM)	367.99	460.49	740.50	784.33
P value	Control group	0.206	< 0.001	< 0.001

[0108] Example 3. Detection of cholic acid conjugated to tryptophan yield by *L. paracasei* Lc19

[0109] Materials: *L. paracasei* Lc19 (*L. paracasei* having the Accession No. CGMCC NO. 17827), cultured in MRS medium.

[0110] Methods: When *L. paracasei* Lc19 was cultured to an OD value of 0.6, 1 mM bile acid and 1 mM tryptophan were added as substrates. After culture for additional 24 hours, 50ul of bacterial solution was taken and mixed with 50ul of methanol by shaking. The mixture was then centrifuged at 12000rpm, and the

supernatant was filtered through a 0.22 µm pore size water-based filter membrane. Mass spectrometry was used to detect the content of cholic acid conjugated to tryptophan. The mass spectrometry conditions were as follows. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) system was employed for the quantification of cholic acid conjugated to tryptophan (TrpCA). The LC-MS/MS system consists of an Acquity ultra-high performance liquid chromatography system (Waters Corporation, Milford, USA) coupled with a Sciex 5500 triple quadrupole linear ion trap mass spectrometer (AB Sciex, Framingham, MA, USA). The chromatographic column used was ACQUITY UPLC CSH C18 (2.1 x 100 mm, 1.7 µm, Waters), with a column temperature of 40 °C and a flow rate of 0.25 mL/min. The injection volume was 5 µL. The mobile phase A was 0.1% formic acid aqueous solution, and the mobile phase B was 0.1% formic acid in acetonitrile. TrpCA was detected using the MRM mode under negative ion conditions. Gradient elution was used for the separation of metabolites: 0-1 min, 40% B; 1-6 min, 40-100% B; 6-7 min, 100% B; 7-8 min, 40% B. Mixed working standard solutions of different concentrations were obtained by gradient dilution (0.1, 1, 10, 100, 1000 nM) to construct a standard curve. CA-d4 (200 nM) was used as an internal standard for content correction. The LC-MS/MS control system utilized the Analyst 1.6.2 version, and quantitative analysis was performed using the MultiQuant software (version 3.0.1).

[0111] Results: *L. paracasei* Lc19 was able to synthesize cholic acid conjugated to tryptophan, as shown in Table 7.

[0112] Table 7. Detection of cholic acid conjugated to tryptophan produced by *L. paracasei* Lc19

Species	Genus	Content of cholic acid conjugated to tryptophan (nmol/L)
<i>L. paracasei</i> Lc19	Lactobacillus	140.53

[0113] Example 4. Effect of *L. paracasei* Lc19 on indicators related to

glucose tolerance in hyperglycemic mice

[0114] Materials: The tested strain was *L. paracasei* Lc19. The amount of bacteria for gavage was set at 2×10^8 CFU/30g body weight, and administrated with a frequency of once a week. The bacterial solution should be cultured in advance, activated every week to ensure freshness, and the concentration was determined separately.

[0115] C57BL/6 mice were purchased from GemPharmatech, maintained at a temperature of 20-24°C, with a constant humidity of 50-60%, and exposed to light for 12 hours from 8:00 to 20:00 with soundproofing and with ad libitum feeding and drinking water. They were acclimated for one week before the experiment. The blood glucose meter was a product of Roche Company in Germany.

[0116] Methods: Male C57BL/6 mice aged 6-8 weeks, weighing 20-22g, were evenly divided into groups based on their body weights: (1) control group, (2) *L. paracasei* Lc19 colonization group, with 9 mice in each group. Gavage was performed twice weekly for 2 consecutive weeks. The control group received an equal volume of saline. Two weeks later, a glucose tolerance test was conducted, and blood glucose levels were measured at different time points (0 min, 30 min, 60 min, 90 min, and 120 min) after glucose gavage. The area of the curve (AOC) was calculated. The GLP-1 and insulin secretion levels were detected using an active GLP-1 detection kit (from Merck) and an insulin detection kit (CUSABIO), respectively, according to the instructions provided in the kits. An additional experimental group was included: after one week of *L. paracasei* Lc19 gavage, mice were euthanized, and their small intestinal segments were excised and the contents removed. The small intestinal contents of the mice were extracted with 20-fold methanol, and mass spectrometry was used to detect changes in the content of cholic acid conjugated to tryptophan in the small intestinal contents of the mice.

[0117] Results: Two weeks after the colonization of *L. paracasei* Lc19, the

content of cholic acid conjugated to tryptophan in mice was increased, and glucose tolerance was significantly improved, as shown in Tables 8-10 and Figure 5.

[0118] Table 8. Detection of cholic acid conjugated to tryptophan in mice colonized with *L. paracasei* Lc19 (The statistical method is a two-tailed unpaired T test.)

Grouping	Content of cholic acid conjugated to tryptophan (nmol/g)
Control group	4.33
<i>L. paracasei</i> Lc19 Group	12.06
P value	< 0.001

[0119] Table 9 Effect of colonization with *L. paracasei* Lc19 on glucose tolerance in mice fed with a high-fat diet (The statistical method was a two-way analysis of variance of duplicate measurements with unpaired T test.)

Grouping	Blood glucose (mg/dL)						
	0 minutes	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes	Curve area
Control group	199.8	434.6	452.2	347.4	246.4	226.4	15426
Lc19	186	369.4	373.6	273.6	220	199.4	10821
P value	0.258	0.012	0.010	0.004	0.140	0.146	<0.001

[0120] Table 10. Effects of colonization with *L. paracasei* Lc19 on glucose-stimulated GLP-1 and insulin production in mice fed with a high-fat diet(The statistical method was a two-way analysis of variance of duplicate measurements with unpaired T test.)

Grouping	GLP-1 (pM)		Insulin (ng/mL)	
	0 minutes	15 minutes	0 minutes	15 minutes
Control group	4.58	11.23	0.71	1.617
Lc19	5.1	16.63	0.689	2.283

P value	0.156	<0.001	0.536	0.001
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[0121] Although the present disclosure has been described with reference to illustrative embodiments, it will be understood by those skilled in the art that various other changes, omissions and/or additions may be made and substantial equivalents may be substituted for elements of the described embodiments without departing from the spirit and scope of the present disclosure. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the disclosure without departing from the scope thereof. Therefore, it is not intended to limit the disclosure to the particular embodiments disclosed for carrying out this disclosure, but that the disclosure will include all embodiments falling within the scope of the appended claims.

Claims

1. *Lacticaseibacillus paracasei* or postbiotics thereof or composition comprising the *Lacticaseibacillus paracasei* or postbiotics thereof for use in generating a cholic acid conjugated to tryptophan.

2. The *Lacticaseibacillus paracasei* or postbiotics thereof or composition comprising the *Lacticaseibacillus paracasei* or postbiotics thereof for use according to claim 1, wherein the *Lacticaseibacillus paracasei* or postbiotics thereof is for use in preventing and/or treating a metabolic disease or for promoting GLP-1 and/or insulin production, and/or for use in maintaining healthy blood glucose level, maintaining healthy blood lipid and/or controlling body fat.

3. The *Lacticaseibacillus paracasei* or postbiotics thereof or composition comprising the *Lacticaseibacillus paracasei* or postbiotics thereof for use according to claim 1 or 2, wherein the *Lacticaseibacillus paracasei* is deposited with the Accession Number CGMCC NO. 17827; optionally, the *Lacticaseibacillus paracasei* is in a form of a powder or a culture solution.

4. The *Lacticaseibacillus paracasei* or postbiotics thereof or composition comprising the *Lacticaseibacillus paracasei* or postbiotics thereof for use according to any one of claims 2-3, wherein the metabolic disease is a GLP-1 related metabolic disease, optionally selected from a group consisting of diabetes or a disease associated with diabetes;

optionally, the diabetes is selected from a group consisting of type 1 diabetes, type 2 diabetes, gestational diabetes, obesity diabetes, autoimmune diabetes and borderline diabetes;

optionally, the disease associated with diabetes is selected from a group consisting of obesity, an obesity-related disorder, metabolic syndrome, diabetic

neuropathy, a kidney disease such as diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, diabetic gangrene, xerostomia, hypoacusis, diabetic cachexia, delayed wound healing, diabetic dyslipidemia, a peripheral blood circulation disorder, non-alcoholic steatohepatitis, pre-diabetes, hyperlipemia, a fatty liver disease, impaired fasting glucose, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, elevated blood fatty acid or glycerol levels, impaired wound healing, glucose intolerance, increased fasting glucose and dyslipidemia, pancreatic beta cell insufficiency, enteroendocrine cell insufficiency, glycosuria, metabolic acidosis, cataract, a diabetic coronary heart disease, a diabetic cerebrovascular disease, a diabetic peripheral vascular disease, metabolic syndrome, atherosclerosis and stroke;

optionally, the obesity is selected from a group consisting of symptomatic obesity, simple obesity, childhood obesity, morbid obesity and abdominal obesity;

optionally, the disease associated with obesity is selected from a group consisting of glucose tolerance, abnormal lipid metabolism, hyperlipidemia, hypertension, heart failure, hyperuricemia, gout, fatty liver, a coronary heart disease, cerebral infarction, sleep apnea syndrome, obesity hypoventilation syndrome and visceral obesity syndrome.

5. The *Lactcaseibacillus paracasei* or postbiotics thereof or composition comprising the *Lactcaseibacillus paracasei* or postbiotics thereof for use according to any one of claims 1 to 4, wherein the *Lactcaseibacillus paracasei* or postbiotics thereof or composition comprising the *Lactcaseibacillus paracasei* or postbiotics thereof is further for use in ameliorating constipation and/or ameliorating inflammatory bowel disease, optionally, the constipation is functional constipation and the inflammatory bowel disease is colitis or Crohn's disease;

optionally, the *Lactcaseibacillus paracasei* or postbiotics thereof is administrated at 1×10^4 - 1×10^{12} cfu/mL, 1×10^4 - 1×10^9 cfu/mL or 1×10^5 - 1×10^8 cfu/mL

viable bacteria;

optionally, the *Lacticaseibacillus paracasei* or postbiotics thereof is administrated orally;

optionally, the composition is a pharmaceutical composition or a food composition;

optionally, the pharmaceutical composition further comprises probiotics, prebiotics and/or a pharmaceutically acceptable carrier, diluent or excipient;

optionally, the food composition further comprises probiotics, prebiotics and/or a food-acceptable carrier, diluent or excipient;

optionally, the pharmaceutical composition is an oral composition, optionally selected from a group consisting of an enteric coated tablet, a granule, a capsule, a tablet, a powder, an oral liquid, a suspension and an emulsion;

optionally, the food composition is a liquid, semi-solid or solid, optionally selected from a group consisting of a dairy product, a confectionery product, a fruit juice and an instant food product;

optionally, a unit dose of the pharmaceutical or food composition comprises 1×10^1 - 1×10^{12} cfu/mL, 1×10^4 - 1×10^9 cfu/mL or 1×10^5 - 1×10^8 cfu/mL viable bacteria.

6. A composition comprising *Lacticaseibacillus paracasei* wherein the composition is a pharmaceutical composition or a food composition, the pharmaceutical composition further comprises another active ingredient for preventing and/or treating a metabolic disease, or the food composition further comprises another food active ingredient for maintaining healthy blood glucose level, maintaining healthy blood lipid and/or controlling body fat.

optionally, the *Lacticaseibacillus paracasei* is deposited with the Accession Number CGMCC NO. 17827;

optionally, the another active ingredient is one or more of a biguanide, a sulfonylurea, a glinide, an alpha-glucosidase inhibitor, a thiazolidinedione and a GLP-1 drug;

optionally, the pharmaceutical composition is an oral composition,

optionally selected from a group consisting of an enteric coated tablet, a granule, a capsule, a tablet, a powder, an oral liquid, a suspension and an emulsion;

optionally, the pharmaceutical composition further comprises probiotics, prebiotics and/or a pharmaceutically acceptable carrier, diluent or excipient;

optionally, the food composition is a liquid, semi-solid or solid, optionally selected from a group consisting of a dairy product, a confectionery product, a fruit juice and an instant food product;

optionally, the food composition further comprises probiotics, prebiotics and/or a food-acceptable carrier, diluent or excipient.

7. A method for producing a cholic acid conjugated to tryptophan, comprising culturing *Lacticaseibacillus paracasei* in a medium in the presence of a bile acid and tryptophan to produce the cholic acid conjugated to tryptophan, optionally, the *Lacticaseibacillus paracasei* is deposited with the Accession Number CGMCC NO. 17827.

8. Use of *Lacticaseibacillus paracasei* for the production of a cholic acid conjugated to tryptophan, optionally, wherein the *Lacticaseibacillus paracasei* is deposited with the Accession Number CGMCC NO. 17827.

9. A method for screening a strain of the genus *Lactobacillus* that produces a cholic acid conjugated to tryptophan, comprising

(1) culturing a strain of the genus *Lactobacillus* in a medium in the presence of a bile acid and tryptophan to obtain a culture supernatant;

(2) measuring the content of the cholic acid conjugated to tryptophan in the culture supernatant; and

(3) selecting the strain of the genus *Lactobacillus* that produces the cholic acid conjugated to tryptophan;

optionally, the method is a method for screening a strain of the genus *Lactobacillus* that promotes GLP-1 and/or insulin production;

optionally, the strain of the genus *Lactobacillus* is *Lacticaseibacillus paracasei*, optionally *Lacticaseibacillus paracasei* deposited with the Accession Number CGMCC NO. 17827.