



Patent Translate

Powered by EPO and Google

Notice

This translation is machine-generated. It cannot be guaranteed that it is intelligible, accurate, complete, reliable or fit for specific purposes. Critical decisions, such as commercially relevant or financial decisions, should not be based on machine-translation output.

DESCRIPTION CN111938158A

A group that prevents the decrease in abundance of Akkermansia muciniphila in the gut

Compounds

[0001]

Technical Field

[0002]

This invention relates to the field of health, particularly to the fields of food, health products and pharmaceuticals within the health field, especially to the field of regulating intestinal microbiota, and specifically to a composition for regulating the abundance of *Akkermansia muciniphila* in the intestine.

[0003]

Background Technology

[0004]

The human gut microbiota plays a vital role in the balance between health and disease.

Microbial dysbiosis is associated with various metabolic disorders.

Akkermansia muciniphila is a Gram-negative anaerobic coccus.

In 2004, Professor Derrien and her team isolated it from the human intestine and named it *Akkermansia muciniphila* [Derrien M. *Akkermansia muciniphila* gen.nov.sp.nov.a human intestinal mucin-degradingbacterium]. Int. J.Syst. Evol. Microbiol. 2004, 54.

[0005]

Low levels of *Akkermansia muciniphila* in the gut may lead to thinning of the mucosal layer, resulting in weakened intestinal barrier function and making it easier for toxins in the gut to enter the body [Brahe et al. Specific gut microbiota features and metabolic markers in postmenopausal women with obesity].

Nutrition & Diabetes, 5(6):e159]. Typically, patients with inflammatory bowel disease or obesity will have a decrease in the amount of *Akkermansia muciniphila* in their bodies. Early mouse studies have shown that *Akkermansia muciniphila* abundance is reduced in obese mice, and feeding them prebiotics can normalize *Akkermansia muciniphila* abundance, thereby improving the metabolic status of mice [Everard A et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity]. Proceedings of the National Academy of Sciences, 2013,110(22):9066-9071].

[0006]

Currently, regulating the gut microbiota structure through prebiotics is the main method to improve the gut microecological structure.

It is generally believed that prebiotics provide "food" for probiotics. Prebiotics can be broken down and absorbed by beneficial bacteria in the intestines, promoting the growth and reproduction of beneficial bacteria. However, because many types of gut probiotics have very similar affinity for common prebiotics, the use of prebiotics can alter the number of bacteria in a large number of gut microbiota, making it impossible to target and proliferate a particular type or class of probiotics. The use of common prebiotics can reduce the levels of Bacteroidetes/Firmwallis, which can lead to rapid obesity. Long-term use may also increase the risk of endocrine and metabolic diseases such as hyperglycemia, hyperlipidemia, and hypertension.

[0007]

Therefore, methods that regulate the abundance of Akkermansia muciniphila in the gut using

prebiotics have drawbacks such as poor specificity and the potential to cause obesity and other diseases.

[0008]

Summary of the Invention

[0009]

To address the shortcomings of existing technologies, this invention proposes to restore the abundance of *Akkermansia muciniphila* by supplementing with L-valine. Unlike the method of regulating *Akkermansia muciniphila* abundance with prebiotics, L-valine is absorbed by the intestines rather than by the gut microbiota, resulting in high biocompatibility. Therefore, the composition of this invention can be used as a food, health product, or medicine to restore *Akkermansia muciniphila* abundance.

[0010]

The purpose of this invention is to provide a composition for preventing the decrease in *Akkermansia muciniphila* abundance, wherein the composition uses L-valine as the active ingredient and has a significant therapeutic effect on preventing the decrease in *Akkermansia muciniphila* abundance in the intestine.

[0011]

To achieve the above objectives, the present invention provides the following technical solution:

[0012]

A composition for preventing a decrease in the abundance of *Akkermansia muciniphila* in the gut, comprising L-valine and pharmaceutical excipients.

Valine is an essential amino acid and is mostly used in nutritional supplements in current technology. There are no reports of using it to prevent a decrease in the abundance of *Akkermansia muciniphila* in the gut.

[0013]

Furthermore, the active ingredient L-valine in the composition of the present invention can be a water-soluble compound, thus it is applicable to a wide range of dosage forms. The dosage form can be selected according to the product use (pharmaceutical, health care or food) and the consumer group. Each dosage form has different advantages and disadvantages.

[0014]

Taking oral liquids as an example, oral liquids have the advantages of small dosage, fast absorption, stable quality, convenient carrying and taking, and easy storage. Adding excipients to oral liquids can improve taste, improve clarity, enhance stability, and improve product quality.

[0015]

Common excipients for oral liquids include one or more of the following: solvents, flavoring agents, tasters, clarifying agents, and preservatives.

[0016]

Taking tablets as an example, tablets have the advantages of accurate dosage, stable quality, and convenient administration, carrying and transportation.

[0017]

Common excipients for tablets include one or more of the following: diluents, binders, lubricants, and disintegrants.

[0018]

Taking granules as an example, granules can be swallowed directly or dissolved in warm

water for drinking. They are convenient to use and carry, and dissolve and are absorbed quickly.

[0019]

Common excipients for granules include one or more of the following: fillers, binders, wetting agents, disintegrants, lubricants, and film coating materials.

[0020]

Taking capsules as an example, capsules mainly improve the stability and bioavailability of drugs.

[0021]

The excipients commonly used in capsule formulations are hard capsule shells or soft capsule shells.

[0022]

The compositions of the present invention can also be formulated into powders.

Powders are convenient for dispensing and taking.

[0023]

Taking beverages as an example, the compositions of the present invention can be made into beverages with different flavors, which will be very popular as daily drinks.

[0024]

Commonly used beverage additives include at least one of clarifying agents, preservatives, and flavoring agents.

[0025]

The compositions of the present invention can also be made into other powders, such as functional milk powder, with the added excipients mainly being milk powder, such as skim milk powder or skim sugar-free milk powder.

[0026]

In summary, compared with the prior art, the present invention achieves the following technical effects:

[0027]

(1) The composition of the present invention can be used to treat or prevent inflammatory bowel disease and obesity by supplementing L-valine, providing a new product for the treatment and prevention of inflammatory bowel disease and obesity;

[0028]

(2) The composition provided by the present invention can prevent the decrease of Akkermansia muciniphila abundance in the intestine. Compared with the method of regulating Akkermansia muciniphila abundance in the intestine by prebiotics, it has the advantages of high specificity and high safety.

[0029]

(3) It has a wide range of applications and can be used in many fields such as food, medicine or health products;

[0030]

(4) It is applicable to a wide range of dosage forms and is easy to promote.

[0031]

Attached Figure Description

[0032]

To more clearly illustrate the technical solutions of the embodiments of the present invention, the accompanying drawings used in the embodiments will be briefly introduced below. It should be understood that the following drawings only show some embodiments of the present invention and should not be regarded as a limitation on the scope. For those skilled in the art, other related drawings can be obtained based on these drawings without creative effort.

[0033]

Figure 1 shows the abundance analysis of *Akkermansia muciniphila* from mouse fecal microbiota 16S rRNA sequencing. The *Akkermansia muciniphila* abundance heatmap was logarithmically processed after multiplying the data by 10000.

[0034]

Figure 2 shows the abundance analysis of *Akkermansia muciniphila* in mouse fecal microbiota obtained by 16S rRNA sequencing, and the percentage of *Akkermansia muciniphila* abundance in the total microbial abundance in the three different feeding groups.

* and ** indicate that the t-test results show a significant difference ($P < 0.05$ and $P < 0.01$, respectively).

N.S.

This indicates that there is no significant difference.

[0035]

Detailed Implementation

[0036]

To enable those skilled in the art to better understand the present invention, the technical solutions of the present invention will be clearly and completely described below with reference to the accompanying drawings of the embodiments of the present invention. Obviously, the described embodiments are only some embodiments of the present invention, and not all embodiments.

Based on the embodiments of the present invention, all other embodiments obtained by those skilled in the art without creative effort should fall within the scope of protection of the present invention.

[0037]

Example 1

[0038]

Fifteen male 8-week-old c57 mice (purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd.) were selected for the experiment and divided into three groups of five mice each. Group A was the control group, fed with a normal diet (Chow), which was purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd., and the formula is

shown in Table 1. Group B was the high-fat diet model group (HFD), fed with a diet containing 60 kcal% high-fat (purchased from Research Diets, catalog number D12492). Research Diets D12492 60 kcal% high-fat diet is generally used as a standard diet for studying obesity and metabolic syndrome.

Group C was fed a high-fat diet containing 60 kcal, and was given 1.5 g/kg of L-valine (V0500 Sigma-Aldrich L-valine reagent grade, purity $\geq 98\%$) in its drinking water daily. The L-valine powder was dissolved in the drinking water and fed to the mice.

Sixteen weeks later, mouse feces were collected using sterile paper, and 16S rRNA fecal microbiota sequencing services were provided by Hangzhou Guhe Information Technology Co., Ltd.

The abundance of the gut microbiota *Akkermansia muciniphila* was compared among the three groups (Figure 1 and Figure 2).

In Figure 1, the abundance of *Akkermansia muciniphila* is represented by different shades of gray; the darker the color, the higher the abundance of *Akkermansia muciniphila*.

In Figure 2, Chow represents the control group fed with normal food, and HFD represents the model group fed with high-fat food containing 60 kcal%.

Val represents the experimental group, which was fed a high-fat diet containing 60 kcal% and was given 1.5 g/kg of L-valine (Val) in their drinking water daily.

The results showed that the abundance of *Akkermansia muciniphila* in the HFD-fed group for 16 weeks was significantly lower than that in the control group fed with normal diet.

The abundance of *Akkermansia muciniphila* in the HFD plus L-valine feeding group for 16 weeks was significantly higher than that in the HFD feeding group for 16 weeks, and then returned to the level of the control group fed with normal diet.

[0039]

Table 1. Standard Feeding Formula (Chow)

[0041]

In summary, it can be determined that the following technical effects can be achieved by using L-valine:

[0042]

1. The effective dose of L-valine for regulating the abundance of *Akkermansia muciniphila* is 1.5 g/kg/day, but this may vary depending on the target population in actual application.

[0043]

2. Supplementing with L-valine can prevent the decrease in the abundance of *Akkermansia muciniphila* in the intestine, restore the abundance of *Akkermansia muciniphila*, and thus improve metabolic status.

[0044]

Although the above experiments only tested the simple compound, based on the known physicochemical properties of L-valine, it can be concluded that the oral dosage forms made from it can achieve the above-mentioned efficacy. The suitable dosage forms and corresponding excipients for L-valine are as follows.

[0045]

This invention can generate multiple implementation methods based on the type of ingredients, content of ingredients, dosage form, etc.

For example:

[0046]

Implementation method 1: An oral liquid with L-valine as the active ingredient;

[0047]

Taking oral liquid as an example, oral liquid is a new dosage form developed on the basis of decoction and injection. It has the advantages of small dosage, fast absorption, stable quality, convenient carrying and taking, and easy storage. It contains a variety of active ingredients, which have a great influence on quality and taste.

Without altering the structure and function of the main active ingredients, the challenge in selecting excipients lies in maximizing the retention of effective components and improving the taste.

Adding excipients to oral liquids can improve taste, clarity, stability, and product quality.

[0048]

Common excipients for oral liquids include: solvents, flavoring agents, tasters, clarifying agents, and preservatives. These excipients can be added simultaneously or one of them can be added. Solvents are mandatory and can be water.

Different combinations of excipients include sweeteners, flavorings, clarifying agents, or preservatives, or combinations of sweeteners and preservatives, with combinations of sweeteners and preservatives being preferred.

Some auxiliary ingredients can both sweeten and enhance the aroma, so in this case, only one auxiliary ingredient needs to be added.

[0049]

For oral liquids, preferably, the sweetener is selected from one or more of protein sugar, xylitol, aspartame, and sucralose.

[0050]

For oral liquids, preferably, the preservative is selected from one or more of parabens, butylated hydroxyanisole, butylated hydroxytoluene, and sorbic acid.

[0051]

Preservatives may include parabens, butylated hydroxytoluene, or sorbic acid, with butylated hydroxytoluene being preferred.

They can also be used in combination, such as a combination of hydroxybenzoate and butylated hydroxytoluene, or a combination of butylated hydroxytoluene and sorbic acid, or a combination of p-hydroxybenzoate and sorbic acid, or a combination of p-hydroxybenzoate, butylated hydroxytoluene and sorbic acid.

[0052]

For oral liquids, preferably, the flavoring agent is fruit flavoring.

[0053]

For oral liquids, preferably, the clarifying agent is one or a mixture of chitosan and gelatin.

[0054]

Implementation method 2: Tablets with L-valine as the active ingredient;

[0055]

Tablets have the advantages of accurate dosage, stable quality, and convenient administration, carrying, and transportation.

[0056]

For tablets, the formulation excipients include one or more of diluents, binders, lubricants and disintegrants, preferably a combination of diluents, binders, lubricants and disintegrants.

[0057]

For tablets, preferably, the diluent is one or more of cellulose and inorganic salts.

Examples of materials used include microcrystalline cellulose, calcium sulfate, calcium hydrogen phosphate, pharmaceutical-grade calcium carbonate, and mannitol, which increase the volume of the raw materials to aid in their molding.

[0058]

For tablets, preferably, the binder is one or more of water, ethanol, sodium carboxymethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, gelatin, and polyvinylpyrrolidone.

[0059]

For tablets, preferably, the lubricant is one or more of magnesium stearate, micronized silica gel, talc, hydrogenated vegetable oil, polyethylene glycol, and magnesium lauryl sulfate.

[0060]

For tablets, preferably, the disintegrant is one or more of low-substituted hydroxypropyl, croscarmellose, and croscarmellose sodium carboxymethyl cellulose.

[0061]

Implementation method 3: Capsules with L-valine as the active ingredient;

[0062]

In this invention, the capsules primarily improve the stability and bioavailability of the drug.

The excipient in the formulation is a capsule shell, which can be a hard capsule shell or a soft capsule shell.

[0063]

Implementation method 4: Granules with L-valine as the active ingredient;

[0064]

Granules can be swallowed directly or dissolved in warm water for drinking. They are convenient to use and carry, and dissolve and are absorbed quickly.

The formulation excipients used in granules are similar to those used in tablets, involving one or more of fillers, binders, wetting agents, disintegrants, lubricants, and film coating materials.

[0065]

For granules, preferably, the filler is one or more of cellulose and inorganic salts.

Examples of materials used include microcrystalline cellulose, calcium sulfate, calcium hydrogen phosphate, pharmaceutical-grade calcium carbonate, and mannitol, which increase the volume of the raw materials to aid in their molding.

[0066]

For granules, preferably, the binder is one or more of water, ethanol, sodium carboxymethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, gelatin, and polyvinylpyrrolidone.

[0067]

For granules, preferably, the wetting agent is water or ethanol or a mixture of both.

For example, it can be one or more of magnesium stearate, micronized silica gel, talc, hydrogenated vegetable oil, polyethylene glycol, and magnesium lauryl sulfate.

[0068]

For granules, preferably, the disintegrant is one or more of low-substituted hydroxypropyl, croscarmellose, and croscarmellose sodium carboxymethyl cellulose.

[0069]

For granules, preferably, the film coating material is one or more of hydroxypropyl methylcellulose, polyethylene glycol, cellulose acetate phthalate, and polyvinyl acetal diethylamine acetate.

[0070]

Implementation method 5: Powder with L-valine as the active ingredient.

[0071]

This invention can also be formulated into a powder, which is convenient for dosage and administration.

[0072]

Taking beverages as an example, the compositions of the present invention can be made into beverages with different flavors, which will be very popular as daily drinks.

[0073]

The excipients used in beverage preparations include at least one of clarifying agents, preservatives, and flavoring agents.

[0074]

The compositions of the present invention can also be made into other powders, such as functional milk powder, with the added excipients mainly being milk powder, such as skim milk powder or skim sugar-free milk powder.

[0075]

The above-mentioned multiple implementation methods can adjust the dosage of the drug in a unit product to suit different uses, such as pharmaceuticals, health products, and food.

[0076]

The above description is only a preferred embodiment of the present invention and is not intended to limit the present invention. Any modifications, equivalent substitutions, improvements, etc., made within the spirit and principles of the present invention should be included within the protection scope of the present invention.