The present invention relates to a composition comprising an effective amount or an effective amount of one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof for reducing uric acid in a subject. The invention also provides a method for the treatment of gout or the amelioration of symptoms related to a high level of uric acid comprising the step of administering or applying the above-mentioned dipeptides to a subject.
COMPOSITION CONTAINING DIPEPTIDE OF HISTIDINE AND ALANINE FOR REDUCING URIC ACID AND METHOD FOR REDUCING URIC ACID USING THE DIPEPTIDE

FIELD OF THE INVENTION

[0001] The present invention relates to a composition and a method for reducing uric acid in a subject. In particular, the composition of the invention comprises one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof, and the method of the invention comprises the steps of administering or applying the dipeptide(s) described above to a subject in need of reduction of uric acid.

BACKGROUND OF THE INVENTION


[0003] With these functions in mind, recent studies in fatigue relieve have led to the development and commercialization of a highly concentrated anserine derived from marine sources that could reduce the content of muscular lactic acid and the level of carnitine phosphokinase, and effectively increase the stress-endurance level of muscle (Kazuo Sakai et al., 2000, “Development of Industrial Refining and Separation Technology for Dipeptides, Anserine and Carnosine, from Fish Boiling Juice and Their Functional Property.” Yaizu Suisan Chemical Co., Ltd.). Anserine and carnosine, being highly stable dipeptides, remain intact under low pH (<3.0), and resist against digestion by peptidase and proteases excreted from pancreas or other digestive organs. The dipeptides would find their way through the intestinal membranes, enter blood stream intact, and exert their function directly upon target organs such as liver, kidney and heart. Other dipeptides, such as carminine, homocarnosine and ophidine, having similar structures to anserine and carnosine are naturally occurring or can be artificially synthesized.

[0004] A high level of uric acid may induce gout with symptoms such as muscle spasm, localized swelling, inflammation, joint pains, muscle fatigue, stress feelings and myocardial infarction. Many commercialized drugs have been used to treat gout, such as Benzbramaron (URINORM), Probenecid, Allopurinol, Bucolome, Cinchophan and Colchicine. These drugs work by inhibiting the formation of uric acid, removing the extra uric acid from the body, acting on the kidneys to help the body to eliminate uric acid, inhibiting the activity of xanthine oxidase for the conversion xanthine to uric acid, and accelerating the excretion of uric acid from the body. However, these uricosuric agents simultaneously exhibit a number of side effects such as urinary calculus, gastrointestinal obstruction, jaundice and anemia. Therefore, while there are numerous agents for treating gout, there is still a need for a new drug or a dietary supplement for reducing the level of uric acid and thereby treating gout and moderating gout-related symptoms.

SUMMARY OF THE INVENTION

[0005] One object of the invention is to provide a composition for reducing uric acid in a subject comprising an effective amount of one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof. The composition of the invention can be used as a medicament for use in the treatment of gout and related symptoms or in the amelioration of symptoms related to a high level of uric acid, or as a dietary supplement.

[0006] Another object of the invention is to provide a method of reducing uric acid in a subject in need thereof, comprising the step of administering or applying an effective amount of one or more dipeptides of the invention to the subject. The method of the invention is useful in the treatment of gout or the amelioration of symptoms related to a high level of uric acid such as muscle spasm, localized swelling, inflammation, joint pains, muscle fatigue, stress feelings, and myocardial infarction.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The invention relates to the novel use of the dipeptide composed of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof for reducing uric acid in a subject. In the first aspect, the invention provides a composition comprising an effective amount of one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof for reducing uric acid in a subject.

[0008] The chemical structures of alanine and histidine are illustrated as follows:

\[
\begin{align*}
\text{alanine} & \quad \text{histidine} \\
\begin{array}{c}
\text{H} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{O}' \\
\text{H} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{CH}_3
\end{array} & \quad \begin{array}{c}
\text{H} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{O}' \\
\text{H} \quad \text{H} \quad \text{C} \quad \text{H}_2 \quad \text{CH}
\end{array}
\end{align*}
\]
The term “effective amount” of the dipeptide according to the invention used herein refers to an amount of the dipeptide applied to a subject leading to a substantial reduction of uric acid in the subject. The term “dipeptide” used herein refers to a peptide that is composed of two amino acid molecules or the functional equivalents thereof linked by a peptide bond. The term “functional equivalent” of an amino acid refers to a compound modified from the amino acid (e.g., an amino acid substituted by one or more substituents) and having a function substantially equivalent to that of the unmodified amino acid. In one embodiment of the invention, the functional equivalent of histidine is methyldihistidine or histamine and the functional equivalent of alanine is γ-aminoobutyric acid. The dipeptide of the invention can be naturally occurring or artificially synthesized. Examples of the dipeptides for use in the invention include, but are not limited to, carnosine (β-alanyl-L-histidine), anserine (β-alanyl-1-methyl-L-histidine), carmine (β-alanylhistamine), homocarnosine (γ-aminoobutyryl-L-histidine) and ophidine (β-alanyl-L-3-methylhistidine), which are commercially available.

Preferably, the composition of the invention comprises two or more dipeptides according to the invention. More preferably, the composition of the invention comprises carnosine and anserine. Carnosine and anserine may comprise about 5-30% w/w and about 95-70% w/w of the total amount of the dipeptides, respectively. Preferably, the composition of the invention comprises, on the basis of the total amount of the dipeptides, about 7% w/w of carnosine and about 90% w/w of anserine.

The composition of the invention can further comprise oligopeptides, free amino acids, carnitine and a pharmaceutically or physiologically acceptable excipient. Suitable pharmaceutically acceptable excipients comprises, but are not limited to, dextrin, lactose, starch, t alc, stearic acid, tartaric acid, alcohol, glycerin, vegetable oils and waxes.

To be used as a medicament, the composition of the invention can be prepared in appropriate pharmaceutical dosage forms, e.g., tablets, powders, granules, capsules, liquid and suspension, (for use via different administration routes) by conventional methods with proper pharmaceutically acceptable excipients.

As a medicament, the composition of the invention may be administered through any suitable routes, such as oral or parenteral route. The dosage of the composition will vary with the species of the dipeptide, the route of administration and the conditions of the subject to be treated, which can be readily determined by skilled physicians. For oral administration, for instance, the composition of the invention is administered to provide an amount of about 8 mg to about 50 mg, preferably about 10 mg to about 45 mg, of the dipeptide per day.

The composition of the invention, when used as a medicament, is useful in reducing uric acid in a subject, such as a mammal, preferably a human. In particular, the composition of the invention is useful in controlling the level of uric acid in a subject suffering from gout and ameliorating symptoms related to a high level of uric acid such as muscle spasm, localized swelling, inflammation, joint pains, muscle fatigue, stress feelings, and myocardial infarction.

For used as a dietary supplement, the composition of the invention can be formulated in a suitable form for oral application, such as tablets, powders, granules, capsules, liquid and suspensions by conventional methods. The dosage of the dietary supplement will vary with the species of the dipeptide and the conditions of the subject to which the dietary supplement is applied. Preferably, the dietary supplement of the invention is applied to provide an amount of about 8 mg to about 50 mg, preferably about 10 mg to about 45 mg, of the dipeptide per day.

Many uricosuric agents known for the treatment of gout, such as Benzbromarone (URINORM), Probencid, Allopurinol, Bucolome, Cinchophan and Colchicine, are commercially available. The composition of the invention can be used in combination with one or more uricosuric agents described above for reducing uric acid. When a combination use is desired, the composition of the invention and the one or more uricosuric agents can be administered or applied sequentially or simultaneously. For instance, the composition of the invention may further comprise one or more uricosuric agents in a single dosage form. Alternatively, the composition of the invention and the one or more uricosuric agents are formulated as separate dosage forms and administered or applied simultaneously or sequentially to a subject.

In another aspect, the invention provides a method for reducing uric acid in a subject in need thereof, comprising the step of administering or applying to the subject an effective amount of one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof. Preferably, the method of the invention comprising the step of administering or applying to the subject the composition according to the invention.

In particular, the method of the invention is useful in the treatment of gout or the amelioration of symptoms related to a high level of uric acid such as muscle spasm, localized swelling, inflammation, joint pains, muscle fatigue, stress feelings, and myocardial infarction. The terms “effective amount,” “dipeptide” and “functional equivalent” used herein are as defined above. Preferably, two or more dipeptides according to the invention of proper ratios are administered into a subject in need of reduction of uric acid. More preferably, about 5-30% w/w of carnosine and about 95-70% w/w of anserine, most preferably, about 7% w/w of carnosine and about 90% w/w of anserine, on the basis of the total amount of the two dipeptides, are administered.

The dipeptide of the invention can be administered or applied to a subject by way of any suitable routes such as oral or parenteral route. The effective amount of the one or more dipeptides for treating a subject with an abnormal level of uric acid varies in accordance with the species of the dipeptide, the route of administration and application and the conditions of the subject to be treated, which can be readily determined by skilled physicians. For an oral administration or application, for instance, the dipeptide may be administered to a subject in an amount of about 8 mg to about 50 mg, preferably about 10 mg to about 45 mg per day.

In one embodiment of the invention, the dipeptide of the invention is administered or applied in combination with one or more conventional uricosuric agents such as Benzbromarone (URINORM), Probencid, Allopurinol, Bucolome, Cinchophan and Colchicine. When a combined administration or application is desired, the dipeptide of the
invention and the one or more uricosuric agents can be administered or applied sequentially or simultaneously. For instance, the dipeptide of the invention may be formulated with the one or more uricosuric agents in a single dosage form. Alternatively, the dipeptide of the invention and the one or more uricosuric agents are formulated as separate dosage forms and administered or applied simultaneously or sequentially to a subject in need thereof.

EXAMPLES

[0021] The present invention will become apparent with reference to the examples below. The examples described below are given by way of illustration only and are not intended to be any limitation to the present invention.

Example 1

[0022] Anserine powder with the trade name “Marine Active” (Yaizu Susan Kagaku Kaisha, Yaizu, Shizuoka prefecture, Japan) containing 5% w/w of a dipeptide mixture (90.9% of anserine and 7.3% of carnosine), 15% w/w of oligopeptides developed from an enzymatic digestion of fish protein, 10% w/w of free amino acids, and 70% w/w of dextrin was filled into gelatin capsules at 250 mg each. A gout patient with a high level of uric acid in serum consumed one capsule before each meal during a period of 24 hours. The level of uric acid in serum was monitored by UroSpeed, a rapid sero-uric acid test strip (Apex Biotechnology Co., Inc. Hsinchu, Taiwan, ROC). The results are shown in Table 1.

| TABLE 1 |
| Influence on uric acid level in serum by Marine Active |
| Patient | Age | Uric acid (mg/dl) before taking Marine Active | Uric acid (mg/dl) after 7 days taking Marine Active |
| XL | 40 | 10.5 | 7.0 |
| CH | 35 | 9.6 | 6.5 |
| HT | 60 | 12.5 | 7.2 |
| HH | 58 | 10.0 | 7.3 |
| LH | 34 | 8.8 | 7.0 |
| CP | 42 | 9.8 | 6.8 |
| CD | 38 | 8.9 | 6.3 |
| CC | 55 | 12.3 | 8.5 |

1. A composition for reducing uric acid in a subject comprising an effective amount of one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof.

2. The composition of claim 1, wherein the functional equivalent of histidine is methylyhistidine or histamine.

3. The composition of claim 1, wherein the functional equivalent of alanine is γ-amino butyric acid.

4. The composition of claim 1, wherein the one or more dipeptides are selected from carnosine, anserine, carnitine, homocarnosine and ophidine.

5. The composition of claim 4, wherein the dipeptides are carnosine and anserine.

6. The composition of claim 5, wherein carnosine and anserine comprise about 5-30% w/w and about 95-70% w/w of the total amount of the dipeptides, respectively.

7. The composition of claim 6, wherein carnosine and anserine comprise about 5-30% w/w and about 90% w/w of the total amount of the dipeptides, respectively.

8. The composition of claim 1, which is administered or applied to the subject by an oral or parenteral route.

9. The composition of claim 1, which is administered or applied to provide an amount of about 8 mg to about 50 mg of the one or more dipeptides per day.

10. The composition of claim 9, which is administered or applied to provide an amount of about 10 mg to about 45 mg of the one or more dipeptides per day.

11. The composition of claim 1, further comprising oligopeptides, free amino acids, carnitine, and a pharmaceutically or physiologically acceptable excipient.

12. The composition of claim 1, which is administered or applied to the subject in combination with uricosuric agents, simultaneously or sequentially.

13. The composition of claim 12, wherein the uricosuric agents are selected from Benz bromomate, Probenecid, Allopurinol, Bucolome, Cinchophan and Colecinic.

14. The composition of claim 1, which is used as a medicament for the treatment of gout or the amelioration of symptoms related to a high level of uric acid selected from...
muscle spasm, localized swelling, inflammation, joint pains, muscle fatigue, stress feelings and myocardial infarction.

15. The composition of claim 1, which is used as a dietary supplement.

16. A method for reducing uric acid in a subject in need thereof, comprising the step of administering or applying to the subject an effective amount of one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof.

17. The method of claim 16, wherein the functional equivalent of histidine is methylhistidine or histamine.

18. The method of claim 16, wherein the functional equivalent of alanine is γ-aminobutyric acid.

19. The method of claim 16, wherein the one or more dipeptides are selected from carnosine, anserine, carcinine, homocarnosine and ophitine.

20. The method of claim 19, wherein the dipeptides are carnosine and anserine.

21. The method of claim 20, wherein carnosine and anserine comprise about 5-30% w/w and about 95-70% w/w of the total amount of the dipeptides, respectively.

22. The method of claim 21, wherein carnosine and anserine comprise about 7% w/w and about 93% w/w of the total amount of the dipeptides, respectively.

23. The method of claim 16, wherein the one or more dipeptides is administered or applied to the subject by an oral or parenteral route.

24. The method of claim 16, wherein the effective amount of the one or more dipeptides is about 8 mg to about 50 mg per day.

25. The method of claim 24, wherein the effective amount of the one or more dipeptides is about 10 mg to about 45 mg per day.

26. The method of claim 16, comprising the step of administering or applying to the subject an effective amount of a composition for reducing uric acid in a subject comprising an effective amount of one or more dipeptides consisting of histidine or the functional equivalent thereof and alanine or the functional equivalent thereof.

27. The method of claim 16, which is used for the treatment of gout or the amelioration of symptoms related to a high level of uric acid selected from muscle spasm, localized swelling, inflammation, joint pains, muscle fatigue, stress feelings and myocardial infarction.

28. The method of claim 16, wherein the one or more dipeptides are administered or applied in combination with uricosuric agents, simultaneously or sequentially.

29. The method of claim 28, wherein the uricosuric agents are selected from Benzbromarone, Probenecid, Allopurinol, Bucolome, Cinchophan and Colchicine.

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