[Fig. 3]

(21) International Application Number:
PCT/KR2007/005919

[74x385](57) Title: GROWTH-ENHANCING YEAST HYDROLYSATE AND HEALTH FOOD COMPRISING THE SAME

(54) Abstract: This present invention discloses yeast hydrolysate to increase bone lengths such as growth plate, tibia, femur, etc. and weight and to stimulate growth hormone release. According to one aspect of the present invention, the yeast hydrolysate acquired by the processes including a hydrolysis step to add 0.1 ~ 3 % (w/v) of proteases to yeast or of autolysis substance of yeast; and a separation step to separate materials with the 10,000-30,000 Dalton molecular weight from the supernatant of the said yeast hydrolysate is suggested. The said yeast hydrolysate is safe and has no side effect for intake.
[DESCRIPTION]

[Invention Title]

GROWTH-ENHANCING YEAST HYDROLYSATE AND HEALTH FOOD COMPRISING THE SAME

[Technical Field]

This invention relates to Growth-Enhancing Yeast Hydrolysate and Health Food Comprising the Same.

[Background Art]

Growth is defined by increase in stature and promoted by nutrition, growth hormone, etc. Especially, a nervous system including brain releasing growth hormone grows remarkably during childhood and becomes slow down afterwards.

Longitudinal growth of tibial bone determines stature and bone structure and growth is controlled by a special mechanism. Especially, growth of epiphyseal growth plate for the tibial bone becomes the most important measure for the longitudinal bone growth procedures (Yang Dong-sik et al., 2003). The growth plate is divided into proliferation zone to proliferate chondrocyte, maturation zone to act on maturity and hypertrophy of the chondrocyte and hypertrophic zone, of which interaction contributes to longitudinal growth of tibial bone (Loveridge, 1999).

Recently, as interests are increased in promotion of growth for the children with short stature, growth hormone injection also attracts increased attention but it may cause some problems such as difficult application and side effects including acromegaly, hypothyroidism, etc. Thus, a method to stimulate growth through foods has been being sought together with supplying nutrition such as vitamins, minerals, etc.

For natural materials reporting growth stimulating effects, there are traditional medicinal herbs first of all. Sung (2005) et al. reported the effects of Nogjungtang (a traditional Korean deer decoction) on growth, feed efficiency, and organ growth in male rats at 5 and 10 week old, and there is a report that GSM containing Eleutherococcus senticosus had a mechanism of action for a growth
stimulating effect on longitudinal bone growth concerning about IGF-I in vivo and in vitro.

On the other hand, as yeast hydrolysate (Saccharomyces cerevisiae), which was acquired by protein hydrolysis enzyme treatment, showed effectiveness in reducing the emotional, physical, and behavioral symptoms of premenstrual syndrome and indicated its potential as an appetite repressant, it is receiving remarkable attention as a functional material for the diet food market.

This inventor et al. have prepared a material to develop the functional food to stimulate growth by producing hydrolysate using yeast that has been utilized for various uses in the food area and measuring its influence on tibial bone longitudinal growth and effect to increase emission of growth hormone.

[Disclosure]

[Technical Problem]

The purpose of the present invention is to provide a natural material having safe growth stimulating effects without any side effect.

[Technical Solution]

In order to achieve the purpose above,

According to one aspect of the present invention,

It is possible to suggest the yeast hydrolysate and its manufacturing method acquired by the processes including a hydrolysis step to add 0.1 ~ 3% (w/v) of proteases to yeast or of autolysis substance of yeast; and

A separation step to separate materials with the 10,000-30,000 Dalton molecular weight from the supernatant of the said yeast hydrolysate.
In addition, according to the other aspect of the present invention, it is possible to suggest a functional food for stimulating growth containing the said yeast hydrolysate.

Moreover, according to another aspect of the present invention, it is possible to suggest a growth stimulator containing the said yeast hydrolysate.

Hereunder, the present invention is more specifically described.

As the yeast has been recognized as GRAS class with no harm to the human body, of which 50% or more consists of good quality protein, plenty of minerals, vitamin B group, etc., it has been used for sources to supply various useful materials such as protein, nucleic acid, enzyme, fat, vitamin, minerals, etc. as well as for alcohol or confectionery industry (Roman et al., Food Biotechnology, 6, 225, 1992).

In addition, the yeast extract produced from hydrolysate with autolysis enzyme of yeast and other proteases has been used for raw materials of fermentation medium of bacteria, seasoning, health foods, etc. (Bioindustry, 14, 53, 1997).

However, the growth stimulating function of the yeast extract produced from yeast hydrolysate or yeast-derived peptides does not have been identified, so the present inventor et al. had firstly confirmed their use for growth stimulating effect by measuring effects of such yeast extract or hydrolysate on the tibial bone longitudinal growth and increase of the growth hormone release.
Even though the practice example of the present invention used *Saccharomyces cerevisiae* as a yeast culture, any edible one would not be restricted. Such yeast culture includes *S. carlsbergensis, S. sake*, etc.

In addition, the said yeast may be of compressed type to be sold for table use, as well as cultured one on the general media. Moreover, autolyzed yeast may be used.

In case of using the yeast in culture solution, it would be better to remove the culture through centrifugal separation, etc., suspend it into the distilled water and apply proteases.

For the said proteases, it is preferable to remove hydrophobic amino acid of the peptide or to produce such a peptide without hydrophobic amino. For such enzymes, it may use several enzymes known as a debittering enzyme.

These include but not limited to Flavourzyme, protamox, ficin, neutrase, etc.

The said enzymes may be added in 0.1 ~ 3% (w/v) concentration of the reaction solution. On 0.1%(w/v) or less concentration as above, reaction is not efficiently processed, while adding more than 3% (w/v) concentration is not economical for reaction yield.

The said hydrolysate reaction is well processed under pH 6-8, 45-55℃ from an aspect of reaction yield.

After hydrolysate reaction, the yeast is centrifugally separated to collect supernatant, from which 10,000-30,000 Daltons peptide/ protein is separated. The present invention has performed ultra filtration for that purpose.
The inventor et al. had administered the yeast hydrolysate produced as above to the male rats to identify its impact. That is, we divided and raised the rats into 4 control groups (8 rats/group) such as negative control (N-control) group, positive control (P-control) group given a daily oral administration of foremilk 1 g/kg, YH-I and YH-2 groups given daily administrations of yeast hydrolysate 0.5 and 1 g/kg, respectively, for 4 weeks and performed biochemical analysis, measurements of tibial bone length, growth hormone, etc.

From the results to compare YH-I and YH-2 groups given daily administrations of yeast hydrolysate and positive control (P-control) group given a daily oral administration of foremilk with the N-control group, test groups (P-control, YH-I, YH-2) showed significant differences on their food efficiency ratios (FER) from the N-control group.

**Example of production for functional beverages:**

- Honey 522 mg
- Chiocticamide 5mg
- Nicotinamide 10mg
- Riboflavin hydrochloric sodium 3mg
- Pyridoxine hydrochloride 2mg
- Inositol 30mg
- Ortho acid 50mg
- Yeast hydrolysate 10mg
- Water 200m-0
In addition, the present invention may suggest a growth stimulator containing the said yeast hydrolysate.

Those medicines containing the yeast hydrolysate of the present invention may be used in forms of oral administration types such as powder, granule, tablet, capsule, suspension, emulsion, syrup, aerosol, etc. and, external application, suppository and sterilization injection by further adding proper carrier, excipients and diluent generally used. For pharmaceutical preparation, it is prepared using diluents or excipients such as filler, extender, binder, moisturizer, disintegrator, surface active agent, etc. that are normally used. Solid medicines for oral administration include tablet, pill, powder, granule, capsule, etc., and they are prepared by mixing at least one excipient such as starch, calcium carbonate, sucrose or lactose, gelatin, etc. with the said extract. Moreover, in addition to the simple excipients, lubricants such as magnesium Stearate talc are used. The pharmaceutical preparations for non-oral administration include sterilized aqueous solution, non-aqueous solution, suspension, oily medicine, lyophilization agent and suppository. For non aqueous solutions and suspensions, vegetable oils such as propylene glycol, polyethylene glycol and olive oil, and ester injection such as ethyolate may be used. For mechanism of suppository, witepsol, macrogol, tween 61, cacao fat, laurin fat, glycelo gelatin, etc. may be used.

Use amount of yeast hydrolysate from the present invention may vary upon age, sex or weight of the patient, but generally 0.01 ~ 1000 mg/kg, preferably 0.1 ~ 500 mg/kg can be administered divided into 1 to several times a day. In addition,
administration amount may be increased or decreased depending on administration path, type and severity of disease, sex, weight, or age, etc. of the patient. Therefore, the said administration amount does not restrict scope of the present invention from any aspect.

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[Description of Drawings]

Fig. 1 is a radiography showing measuring parameters of the shapes of femur bone and tibial bone,


Fig. 2 is a graph showing effects of the yeast hydrolysate from the present invention versus against weight change,

Fig. 3 is a graph showing effects of the yeast hydrolysate from the present invention on the tibia, femur, and proximal epiphysis lengths,

Fig. 4 is a graph showing effects of the yeast hydrolysate from the present invention on the growth hormone level, and

Fig. 5 is a graph showing distribution of molecular weights for fractions acquired from ultra filtering of the yeast hydrolysate from the present invention, where distribution of molecular weights for the yeast hydrolysates having 5000 or less, 5000-10000 and 10000-30000 molecular weights are indicated.

[Mode for Invention]

Hereinafter, the present invention will be more specifically described by the examples of practice, however, the present invention will not be limited to such examples, and any party in the similar industry might know that various types of modifications and application may be available within the philosophy and scope of the present invention based on detail description and scope of claims of the present invention, and such modifications and application are included in the scope of the present invention.

Example 1: Production of the Yeast Hydrolysates

The inventor et al. suspended 8g compressed yeast into 100 ml distilled
water to adjust pH to 6-8, added 1.0% of proteases (Flavourzyme, Novozymes Korea Limited, 1000 LAPU/g) and hydrolyzed it at 50°C for 48 hours. We separated it centrifugally, gathered and dried fragments in 10,000-30,000 molecular weights from supernatants using ultra filtering membrane (PM -10 & -30), and called it as yeast hydrolysate for using the following experiments.

Example 2: Animal Test

Test Animals

For test animals, Sprague-Dawley male rats (3 weeks old) had been purchased from Jungang Test Anima (Seoul), housed in stainless steel cages with 2 rats in one cage. The colonies were bred with solid diet (Samyang Co.) at 23±1°C with 60% atmospheric humidity for 3 days before the experiment, and divided into 4 control groups by the randomized block design such as control group, positive control (P-control) group given a daily oral administration of foremilk 1 g/kg, YH-I and YH-2 groups given daily administrations of yeast hydrolysate 0.5 and 1 g/kg, respectively, for 4 week experiments. Every group had 8 rats.

AIN-93 basic diet was freely administered. Food intake during the experiments had been acquired from the average daily food intake calculated from total food intake for 1 week unit. Weight had been measured with scale at same time everyday, and feed efficiency ratio (FER had been calculated with weight increase against the measured food intake.

Biochemical Analysis

At the end date of the 4 week experiment, test animals had been etherized, of which blood had been collected into heparinized tube, centrifugally separated at 3,000 rpm for 15 minutes and used as analysis sample. After collecting blood, the rats had been cut the abdomen open, of which livers, kidneys and spleens had been promptly extracted and weighed. Triglycerides (TG), total cholesterol (TC) and HDL-cholesterol of the blood plasma had been measured using a blood-analyzer (Spotchem, KDK Co., Japan) and LDL-cholesterol levels were calculated according to the method of Friedwald et al. (1972) as follows: LDL-cholesterol = total cholesterol - HDL-cholesterol - (triglycerides /5).

Measurement of Tibial Bone Length
Before and right after the experiments, the rats were etherized and their tribia, i.e. a tribial bone, femur and proximal epiphysis lengths had been measured. On X-ray measurement, distance to the platform was 25 cm, and the radiographs were taken at 25 kV and 15 second exposure. Measurements of individual tibial bone lengths were performed on the radiographs using a microfilm reader (NCR model 605-0070 837). Total tibial length was measured as the length of the joint as shown on Fig. 1 and femur and proximal epiphysis lengths were also measured.

Growth Hormone Measurement

At the end of 4 week experiment, quantity of growth hormone had been measured by ELISA method, using growth hormone kit (Amersham Pharmacia Biotech, UK) and as previously described (Johansen et al. 1999).

Statistical Analysis

Test results were statistically processed using SPSS (SPSS Inc., USA), and expressed as the mean and standard deviation (Mean ± SD). The significance of the differences was verified using Duncan's multiple range tests within values of p<0.05 after ANOVA test.

Body Weight Change and Food Intake

The food intake, body weight gain and food efficiency ration of the rats bred for 4 weeks are shown on Table 1. The YH-I and YH-2 groups given daily administrations of yeast hydrolysate showed significant increases in body weight gain as compared to the N-control group (p<0.05); however there was no significant difference in body weight gain between the YH-I and YH-2 groups. Food efficiency ratio showed significant differences between the N-control group and the experiment groups (P-control, YH-I, and YH-2 groups), but there were no significant differences among the experiment groups.

[Table 1]
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-Control group</th>
<th>Positive-control group</th>
<th>YH-I</th>
<th>YH-2</th>
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</thead>
<tbody>
<tr>
<td>Body weight gain (g/day)</td>
<td>$3.4 \pm 0.2^b$</td>
<td>$6.08 \pm 0.71^a$</td>
<td>$6.39 \pm 0.46^a$</td>
<td>$5.96 \pm 0.62^b$</td>
</tr>
<tr>
<td>Food intake (g/day)</td>
<td>$18.07 \pm 1.74^b$</td>
<td>$21.50 \pm 3.03^a$</td>
<td>$20.83 \pm 1.89^a$</td>
<td>$20.18 \pm 1.75^a$</td>
</tr>
<tr>
<td>FER $^1$</td>
<td>$0.22 \pm 0.01^b$</td>
<td>$0.28 \pm 0.04^a$</td>
<td>$0.30 \pm 0.02^a$</td>
<td>$0.30 \pm 0.03^a$</td>
</tr>
</tbody>
</table>

$^1$FER: Food efficiency ratio = body weight gain/food intake.

Values are mean ± SD for 8 rats.

Means with different superscript letters within a row are significantly different at p<0.05 by Duncan’s multiple range tests.

**Organ Weights and Plasma Lipids**

From the comparison results of individual organs extracted from rats bred for 4 week (Table 2), weights of livers, kidneys and spleens had no significant difference from three groups. In other words, as no unusual alteration such as organ hypertrophy or atrophy had been observed in case of oral doses of yeast hydrolysate, safety of the yeast hydrolysate from the present invention could be confirmed.

From the measurement results of contents for glucose, triglycerides, cholesterol, HDL-cholesterol, and LDL-cholesterol out of blood plasma (Table 3), there was no significant difference from contents of blood plasma cholesterol, HDL-cholesterol and LDL-cholesterol among 3 groups.

[Table 2]
<table>
<thead>
<tr>
<th>Parameter</th>
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<th>YH-2</th>
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<tr>
<td>Liver</td>
<td>3.68±0.18 a</td>
<td>3.30±0.18 b</td>
<td>3.21±0.13 b</td>
<td>3.23±0.13 b</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.93±0.13</td>
<td>0.87+0.04</td>
<td>0.83±0.04</td>
<td>0.83±0.05</td>
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<tr>
<td>Spleen</td>
<td>0.20±0.03</td>
<td>0.21+0.01</td>
<td>0.23±0.02</td>
<td>0.23±0.03</td>
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</table>

Values are mean ± SD for 8 rats.

Means with different superscript letters within a row are significantly different at p<0.05 by Duncan's multiple range tests.

[Table 3]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-Control group</th>
<th>Positive-control group</th>
<th>YH-I</th>
<th>YH-2</th>
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<tr>
<td>Glucose</td>
<td>121.50±14.94</td>
<td>120.16±21.45</td>
<td>116.38±14.02</td>
<td>122.14±12.56</td>
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<tr>
<td>Triacylglycerol (mg/dl)</td>
<td>67.75±8.79</td>
<td>70.20±7.94</td>
<td>72.17±6.51</td>
<td>73.00+4.46</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>58.00±8.21</td>
<td>56.78+4.34</td>
<td>57.00+11.42</td>
<td>60.43±6.66</td>
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<tr>
<td>HDL-cholesterol</td>
<td>16.75±3.21</td>
<td>18.90±4.45</td>
<td>18.67±3.84</td>
<td>19.86±5.67</td>
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<tr>
<td>LDL-cholesterol</td>
<td>27.70+4.65</td>
<td>23.06+4.12</td>
<td>23.90+6.45</td>
<td>25.97+4.36</td>
</tr>
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</table>

Values are mean ± SD for 8 rats.

Means with different superscript letters within a row are significantly different at p<0.05 by Duncan's multiple range tests.

Increase in Body Weight and Tibial Bone Longitudinal Growth

From the measurement results for increases in body weight for 4 weeks (Fig. 2), N-control group showed 208.3 g, P-control group 237.2 g, YH-I group 230.6 g and YH-2 group 233.1 g of body weight, respectively; there was significant
difference between N-control group and the experiment groups (P-control, YH-I, YH-2), however no significant difference among the experiment groups (P-control, YH-I, YH-2) and N-control group (p<0.05).

From the measurement results of tibial bone lengths (Fig. 3), P-control, YH-I and YH-2 had tibial bone increment value of 0.44 mm/day, 0.47 mm/day and 0.49 mm/day, respectively, while the tibial bone growth of N-control group was 0.37 mm/day. The femur bone longitudinal growth increment values were 0.43, 0.52, and 0.55 mm/day for the P-control, YH-I, and YH-2 groups respectively, and that of the N-control group was 0.42 mm/day. The YH-I and YH-2 groups’ increment values for tibial and femur bone growth were significantly different than the N-control group (p<0.05); however, there was no significant difference between the P-control group and N-control group.

From the measurement results of proximal epiphysis, (Fig. 3), the experiment groups, YH-I (0.62 mm) and YH-2 (0.56 mm) had significant difference from N-control group with 0.17 mm of growth plate height.

Growth Hormone
From the measurement results of growth hormone after 4 weeks (Fig. 4), YH-I (1.77 ng/mL) and YH-2 (2.10 ng/mL) groups showed significant different concentration of growth hormone comparing to that of N-control group (0.82 ng/mL). YH-I and 2 groups showed also significant different growth hormone concentration from P-control group.

[Industrial Applicability]

According to the present invention, the safe yeast hydrolysate having growth stimulating effects without any side effect may be provided. As it has effects to increase growth hormone release, tibial bone length and body weight, it would be useful for health foods or medicines for stimulating growth.
[CLAIMS]

[Claim 1]
The yeast hydrolysate acquired by the processes including a hydrolysis step to add 0.1 ~ 3\% (w/v) of proteases to yeast or of autolysis substance of yeast; and a separation step to separate materials with the 10,000-30,000 Dalton molecular weight from the supernatant of the said yeast hydrolysate.

[Claim 2]
According to Claim 1, the yeast hydrolysate, for which the said proteases removes hydrophobic amino acid of the peptide or produces such a peptide without hydrophobic amino.

[Claim 3]
According to Claim 1, the yeast hydrolysate, for which the hydrolysis is performed at pH 6-8, 45-55 °C.

[Claim 4]
The manufacturing method of yeast hydrolysate, including a hydrolyze step to add 0.1 ~ 3\% (w/v) of proteases to yeast or of autolysis substance of yeast; and a separation step to separate materials with the 10,000-30,000 Dalton molecular weight from the supernatant of the said yeast hydrolysate.

[Claim 5]
According to Claim 1, the manufacturing method of yeast hydrolysate, for which the said proteases removes hydrophobic amino acid of the peptide or produces such a peptide without hydrophobic amino.

[Claim 6]
According to Claim 1, the manufacturing method of yeast hydrolysate, for which the hydrolysis is performed at pH 6-8, 45-55 °C.
[Claim 7]

The functional foods for growth stimulation containing the yeast hydrolysate according to Claim 1.

[Claim 8]

The growth stimulating medicines containing the yeast hydrolysate according to Claim 1.
Fig. 5

A) UF Fraction (>10kDa)
- 112kDa
- 22.8kDa
- 5.9kDa
- 0.36kDa

B) UF Fraction (5~10kDa)

C) UF Fraction (<5kDa)
INTERNATIONAL SEARCH REPORT

PCT/KR2007/005919

A. CLASSIFICATION OF SUBJECT MATTER

A23J 1/18(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 A23J 1/18, A23L 1/29, A61K 35/74, C12P 19/04, C12P 19/34

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

Korean Utility models and applications for Utility models since 1975
Japanese Utility models and applications for Utility models since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKIPASS(KIPO internal) & keyword yeast, protease, filter, and Mw

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>KR 10-2005-01 10413 A (IL-YANG PHARM CO., LTD) 23 November 2005</td>
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<td>US 6,444,448 B1 (RAGINI WHEATCROFT et al) 03 September 2002</td>
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Further documents are listed in the continuation of Box C

See patent family annex

*A* Special categories of cited documents

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

18 JULY 2008 (18 07 2008)

Date of mailing of the international search report

18 JULY 2008 (18.07.2008)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 139 Sounsaro, Seogu, Daejeon 302-701, Republic of Korea

Facsimile No 82-42-472-7140

Authorized officer

Chio Jun Ho

Telephone No 82-42-481-5569

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