DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date:

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	Salacia oblonga (Celastaceae) extract
Firm:	NutriScience Innovations, LLC
Date Received by FDA:	December 22, 2000
90-Day Date:	March 22, 2001

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on pubic display in docket number 95S-0316 after March 22, 2001.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT96

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

MAR 7 2001

Jacob Pallathra
NutriScience Innovations, LLC
2226 Black Rock Turnpike, Suite 206
Fairfield, Connecticut 06430

Dear Mr. Pallathra:

This is in response to your letter dated December 18, 2000 submitted to the Food and Drug Administration (FDA) making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)). Your letter notified FDA of your intent to market a new dietary ingredient, *Salacia oblonga* (Celastraceae) extract.

You state in your submission that "The material would contribute to the human health as illustrated in the attached confidential reference (1) with which our contracted extract manufacturer in Japan who found an active ingredient in the extract, which might be effective as a health ingredient in maintaining blood sugar as well as dieting agent, filed in February 2000 for its US patent application." Reference (1) refers to the new dietary ingredient as an "antidiabetic" agent. Under 21 U.S.C. 321(g)(1)(B), a drug is defined as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. You indicate in your submission that you will suggest to consumers that *Salacia oblonga* (Celastraceae) extract be used to maintain blood sugar and as an antidiabetic agent. These representations suggest that your product is intended to treat diabetes mellitus and therefore, is subject to regulation as a drug under 21 U.S.C. 321(g)(1)(B) and not as a dietary supplement. See 21 CFR § 101.93(g). If you wish *Salacia oblonga* (Celastraceae) extract to be evaluated for its use in the treatment of diabetes mellitus, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, HFD-310, 7520 Standish Place, Rockville, Maryland 20855.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under

21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

As we have stated above, your product containing *Salacia oblonga* (Celastraceae) extract is subject to regulation as a drug. Nonetheless, we have carefully considered the information in your submission concerning whether a dietary supplement containing *Salacia oblonga* (Celastraceae) extract will reasonably be expected to be safe if it were able to be marketed as a dietary supplement. We have significant concerns about the adequacy of the evidence on which you rely to support your conclusion that a dietary supplement containing *Salacia oblonga* (Celastraceae) extract will reasonably be expected to be safe. We explain our concerns below.

The submission does not adequately describe the new dietary ingredient that is the subject of the submission. The "active ingredient" in *Salacia Oblonga* was presented as $C_9H_{19}S_20_9$. However, throughout the notification, the *Salacia oblonga* (Celastraceae) extract was referred to as "Novel Compound S," "Novel Compound SP," "the test drug," and "Product of the present invention." These descriptions of the new dietary ingredient provide no information on the identity or character of this ingredient. Further, the notification discusses several different extraction methods for the dietary ingredient that may produce variations in the composition of the finished new dietary ingredient. As discussed above, 21 U.S.C. 350b(a)(2) states that a dietary supplement containing a new dietary ingredient is adulterated unless there is a history of use or other evidence of safety establishing that it will reasonably be expected to be safe. The manufacturer must submit to FDA the information that is the basis for it having determined that the dietary supplement will be reasonably expected to be safe. It is not possible to have a reasonable expectation of safety without knowledge of the nature and identity of the new dietary ingredient. The descriptions of your new dietary ingredient do not address the specific qualitative and quantitative characteristics of the dietary ingredient that would enable a determination to be made that there is a reasonable expectation of safety. Such information is a necessary prerequisite to meeting the requirements set forth in 21 U.S.C. 350b(a)(2).

Your submission contains evidence of history of use and other information that you assert is an adequate basis to conclude that the type of dietary supplement product containing the new dietary ingredient will reasonably be expected to be safe. However, several animal studies contained in your notification were incomplete, e.g., failed to identify the level of exposure to the substance, the nature of the actual substance administered, or the species of animals exposed to the substance. Therefore, these studies were of limited utility for assessing the safety of *Salacia oblonga* (Celastraceae) extract. Further, the two human studies contained in the submission provide little support for concluding that consumption of dietary supplements containing this ingredient will reasonably be expected to be safe in healthy people. These studies were not designed nor intended to examine the adverse or toxicological affects of *Salacia oblonga* (Celastraceae) extract. Moreover, how the substance that was administered

to the subjects compared to the new dietary ingredient *Salacia oblonga* (Celastraceae) extract was not addressed in the notification. These studies used the substance as a therapy for persons with diseases. Such studies have limited utility for determining whether the chronic or long-term use of a substance as an ingredient in dietary supplements is safe.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that *Salacia oblonga* (Celastraceae) extract, when used under the recommended or suggested conditions of use in the labeling of your product, will reasonably be expected to be safe. In addition, because the information in your submission indicates that your product is a drug and not a dietary supplement, not only would your product be subject to regulation as a drug if marketed, but, even insofar as it might be argued that your product is a dietary supplement, it could be deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) (section 402(f)(1)(B) of the Act). In any event, you are not prohibited from submitting a new premarket notification for *Salacia oblonga* (Celastraceae) extract under 21 U.S.C. 350b(a)(2), if you deem such resubmission appropriate.

Should you have any questions concerning this matter, please contact us at (202) 205-4168.

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
Director
Division of Standards and Labeling
Regulations
Office of Nutritional Products, Labeling, and
Dietary Supplements
Center for Food Safety and Applied Nutrition

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

JAN 18 2001

Jacob Pallathra
President
NurtiScience Innovations, LLC
2226 Black Rock Turnpike, Suite 206
Fairfield, Connecticut 06430

Dear Mr. Pallathra:

This is to inform you that the notification, dated December 18, 2000, you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on December 22, 2000. Your notification concerns the substance called "Salacia oblonga (Celastaceae) extract" that you assert is a new dietary ingredient.

In accordance with 21 C.F.R. § 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., after March 7, 2001), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains "Salacia oblonga (Celastaceae) extract."

Please note that the acceptance of this notification for filing is a procedural matter and thus, does not constitute a finding by FDA that the new dietary ingredient or the dietary supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. As another procedural matter, your notification will be kept confidential for 90 days after the filing date. After March 22, 2001, your notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any information that is trade secret or otherwise commercial confidential information in the notification will not be disclosed to the public.

Please contact us at (202) 205-4168, if you have any questions concerning this matter.

Sincerely,

Margaret C. Carlson
(Acting) Leader
Dietary Supplements Team
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

NutriScience Innovations, LLC
2226 Black Rock Turnpike, Suite 206 • Fairfield, Connecticut 06430, U.S.A.
Tel: (203) 334-3535 • Fax: (203) 366-1850
e-mail: sales@nutriscienceusa.com

Date: **December 18, 2000**

To: **The Secretary of Health and Human Services**
Office of Special Nutritionals (HFS-450) Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C St. SW. Washington, DC 20204

Subject: **Premarket Notification for a New Dietary Ingredient-Salacia Oblonga**

Dear Sir,

In compliance with the Section 8 of Dietary Supplement Health and Education Act of 1994, we hereby file to the Secretary of Health and Human Services the premarket notification for the new dietary ingredient as follows:

Notifying party:

Jacob Pallathra

NutriScience Innovations, LLC
2226 Black Rock Turnpike, Suite 206, Fairfield, Connecticut 06430

Tel: 203-366-1820, Fax: 203-366-1850, Email: sales@nutriscienceusa.com

The New Ingredient:

Salacia oblonga (Celastaceae) extract

We, as importer and distributor of the said new ingredient, called, have the intention to put this material into interstate commerce in the United States of America after 75 days of this filing. The said herbal material had been in use historically in India, Sri Lanka and other South East Asian countries. The material would contribute to the human health as illustrated in the attached confidential reference (1) with which our contracted extract manufacturer in Japan who found an active ingredient in the extract, which might be effective as a health ingredient in maintaining blood sugar as well as dieting agent, filed in February 2000 for its US patent application.

NutriScience Innovations, LLC
2226 Black Rock Turnpike, Suite 206 • Fairfield, Connecticut 06430, U.S.A.
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The attached reference data (1), (2) and (3) shall suggest that the applied ingredient be reasonably safe for dietary supplement with our suggested use of 60 mg at a time before each meal or 180 mg a day.

We would appreciate your acknowledgment of the receipt of this filing.

Thank you,

Jacob Pallathra
President

Encl. 3 copies of this notice and Reference data (1), (2) and (3)

Reference data (1): 'Compound with Alpha-Glucosidase inhibiting Action and Method for Producing the Same'

Reference data (2): 'Development and Evaluation of a Hypoglycemic tablet with the herb Salacia Prinoides'

Reference data (3): 'Safety Document of Salacia oblong extract'

COMPOUND WITH α-GLUCOSIDASE INHIBITING ACTION AND METHOD FOR PRODUCING THE SAME

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a novel compound obtained from a natural plant and more particularly to a compound which is extracted from a woody climbing plant belonging to the Celastaceae family and inhibits the activity of α-glucosidase, and further to an antidiabetic and dieting agent containing the compound and a method for producing such a compound.

2. Prior Art

In recent years, among therapeutic drugs classified as antidiabetic agents, α-glucosidase inhibitors which inhibit the activity of α-glucosidase have been widely used in the treatment of diabetes and prediabetes. α-glucosidase is an enzyme that breaks down disaccharides or trisaccharides and glucides such as starch, etc., that are present on the mucous membranes of the digestive tract.

As universally known, natural medicines and medicinal foodstuffs, which can be safely and easily supplied in the diet and can inhibit the onset of hyperglycemia, are constantly in demand.

Accordingly, natural drugs used in various traditional systems of medicine around the world have attracted attention as a means of developing natural medicines that do not originate in chemically synthesized produots.

In research and development for developing such natural medicines, the inventor of the present invention has made special efforts in the development of antidiabetic agents.

In this research, the inventor has focused special attention on Salacia reticulata. Salacia reticulata belongs to the Celastaceae family, known in Singhalese as Kotala himbutuwel, which

has been used since ancient times in the traditional medicine of India and Sri Lanka, i.e. in the Ayurvedic medical tradition. In rat experiments by the inventor, an aqueous extract (water-soluble fraction) of this substance has shown a superior effect in inhibiting hyperglycemia following sucrose or maltose loading (i.e., this substance has strongly inhibited the increase of blood sugar levels after the administration of sucrose or maltose in rats). In other words, the inventor has ascertained that the above-described extract is effective in inhibiting the activity of α-glucosidase, an enzyme that as described above breaks down disaccharides, etc.

Furthermore, the inventor has also ascertained that an aqueous extract of Salacia reticulata belonging to the Celastaceae family inhibits the activity of α-glucosidase, i.e., maltase and sucrase, present in the intestines of rats (the fraction inhibited rat intestinal maltase and sucrase).

Furthermore, the present inventor is investigating the active principle that manifests the hyperglycemia-inhibiting effect in Salacia reticulata of the Celastaceae family.

The inventor has also screened plants other than Salacia reticulata, which is a plant belonging to the above-described Celastaceae family, in a search for plants that inhibit the activity of α-glucosidase.

SUMMARY OF THE INVENTION

As a result, the inventor discovered that there is an extremely strong α-glucosidase inhibiting effect in aqueous extracts of Salacia prinoides and Salacia oblonga belonging to the Celastaceae family, and especially in an aqueous extract of the former plant.

More specifically, the inventor, by extracting and fractionating Salacia prinoides, succeeded in discovering a novel compound which has an inhibitory effect against isomaltose (a type of disaccharide) that is more than 200 times stronger than that of the α-glucosidase inhibiting agent Acarbose (manufactured by Bayer Corp., Trademark *Glucobay*), which is a commercially marketed drug. The Acarbose is a type of sugar that is, like antibiotics, produced by the genus Actinoplanes (a certain type of Actinomyces).

The present invention was created based upon these findings.

Accordingly, the object of the present invention is to provide a novel compound which is extracted from the woody climbing plants Salacia prinoides and Salacia oblonga and is superior in terms of its characteristic of inhibiting the activity of α-glucosidase (hereafter this compound may be referred to as an "α-glucosidase inhibitor").

Another object of the present invention is to provide an antidiabetic agent or dieting agent which utilizes the above-described compound having the effect in inhibiting α-glucosidase (which is an enzyme that breaks down disaccharides, etc. that are present on the mucous membranes of the digestive tract).

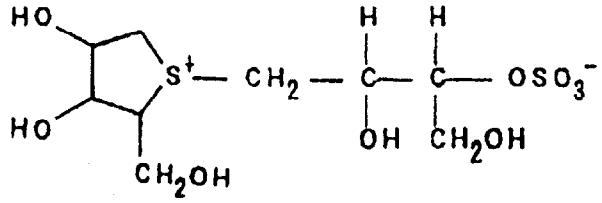
Still another object of the present invention is to provide a method for producing or extracting the above-described compound that has the superior characteristics of inhibiting α-glucosidase activity.

In the present invention, the above-described novel compound (α-glucosidase inhibitor) that has the superior characteristic of inhibiting α-glucosidase activity is obtained by extraction and fractionation from plants belonging to the natural plant Celastaceae family, i.e., Salacia prinoides and/or Salacia oblonga, which have been utilized as natural drugs. Accordingly, the present invention provides an antidiabetic agent and dieting agent that are superior in terms of safety compared to chemically synthesized products.

More specifically, the present invention provides the compound itself that is expressed by the Chemical Structural Formula shown below, which was discovered in the woody climbing plants Salacia prinoides or Salacia oblonga. In the following description, the compound expressed by the Chemical Structural Formula shown below may be referred to as the "novel compound SP (SP merely called after Salacia Prinoides)".

(to next page)

Chemical Structural Formula



Furthermore, the present invention provides an antidiabetic agent which utilizes the property of effectively inhibiting the activity of α-glucosidase (an enzyme that breaks down disaccharides, etc.) shown by the compound expressed by the above Chemical Structural Formula. The present invention further provides a dieting agent used to prevent obesity caused by excessive nutrition, which utilizes the α-glucosidase inhibiting effect of the compound shown by the above Chemical Structural Formula in order to prevent the breakdown of various types of glucides and oligosaccharides (disaccharides or trisaccharides) ingested in meals into monosaccharides and the absorption of such monosaccharides in the body. These applied products were not known at the time of the previous research and development work concerning Salacia reticulata.

Moreover, the present invention provides a method for extracting the novel compound expressed by the above Chemical Structural Formula which is superior in terms of its characteristic of inhibiting the activity of α-glucosidase. In this method, Salacia prinoides and/or Salacia oblonga of the Celastaceae family are subjected to an extraction process using heated methanol, the methanol extract thus obtained are subjected to a partition treatment using ethyl acetate and water, and the portion migrating into the water is then subjected to a fractionation treatment by means of chromatography.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an X-ray analysis diagram of the novel compound SP according to the present invention; and

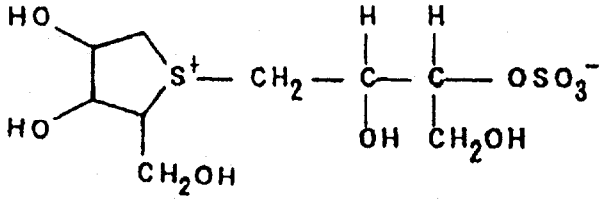
Figure 2 is a model diagram of the novel compound SP according to the present invention.

DETAILED DESCIPTION OF THE PREFERRED EMBODIMENTS

The present invention will be described in detail below.

As described above, the object of the present invention is to discover the true compound that inhibits the activity of α-glucosidase (which is an enzyme that breaks down disaccharides, etc.) by applying extraction and fractionation processes using, as a basis, Salacia prinoides and/or Salacia oblonga that belong to the Celastaceae family (whose plants are used as components of natural medicines). It is another object of the present invention to provide a safe and highly potent antidiabetic agent and dieting agent of the natural drug type which use, as a basis, the thus discovered novel compound (that shows superior inhibition of α-glucosidase activity).

In research and development aimed at discovering the active principle (active substance) that inhibits the activity of α-glucosidase using Salacia prinoides and/or Salacia oblonga of the Celastaceae family as a base, the present inventor succeeded in discovering the novel compound SP expressed by the Chemical Structural Formula shown as:



Further, the inventor succeeded in developing an antidiabetic agent and a dieting agent that uses the properties of the novel compound SP which is the above-described active principle (active substance), and also in establishing an effective and economical method for extracting the novel compound S.

The novel compound SP of the present invention which is expressed by the above Chemical Structural Formula has the property of effectively inhibiting the activity of α-glucosidase, and is useful as an antidiabetic agent. In other words, the novel compound SP of the present invention inhibits the breakdown of oligosaccharides (disaccharides and trisaccharides) such as sucrose, maltose, etc. into monosaccharides that is caused by α-glucosidase, and inhibits

the absorption of monosaccharides such as glucose, mannose, etc. in the body, so that blood sugar levels are prevented form rising. Accordingly, the compound of the present invention is extremely useful as an antidiabetic agent.

Furthermore, since the novel compound SP of the present invention inhibits the activity of α-glucosidase which is an enzyme that breaks down glucides such as starch, etc. and oligosaccharides (disaccharides and trisaccharides), the compound prevents the breakdown of glucides and oligosaccharides into monosaccharides such as glucose, etc. Accordingly, the absorption of excessive glucose in the body is prevented. As universally known, glucose absorbed in the body is converted into glycogens and neutral lipids by insulin and then accumulates as body fat or organ fat, thus causing obesity. As is clear from the above description, the novel compound SP of the present invention is extremely useful as a dieting agent. The novel compound SP can also be obtained by extraction and fractionation from Salacia reticulata.

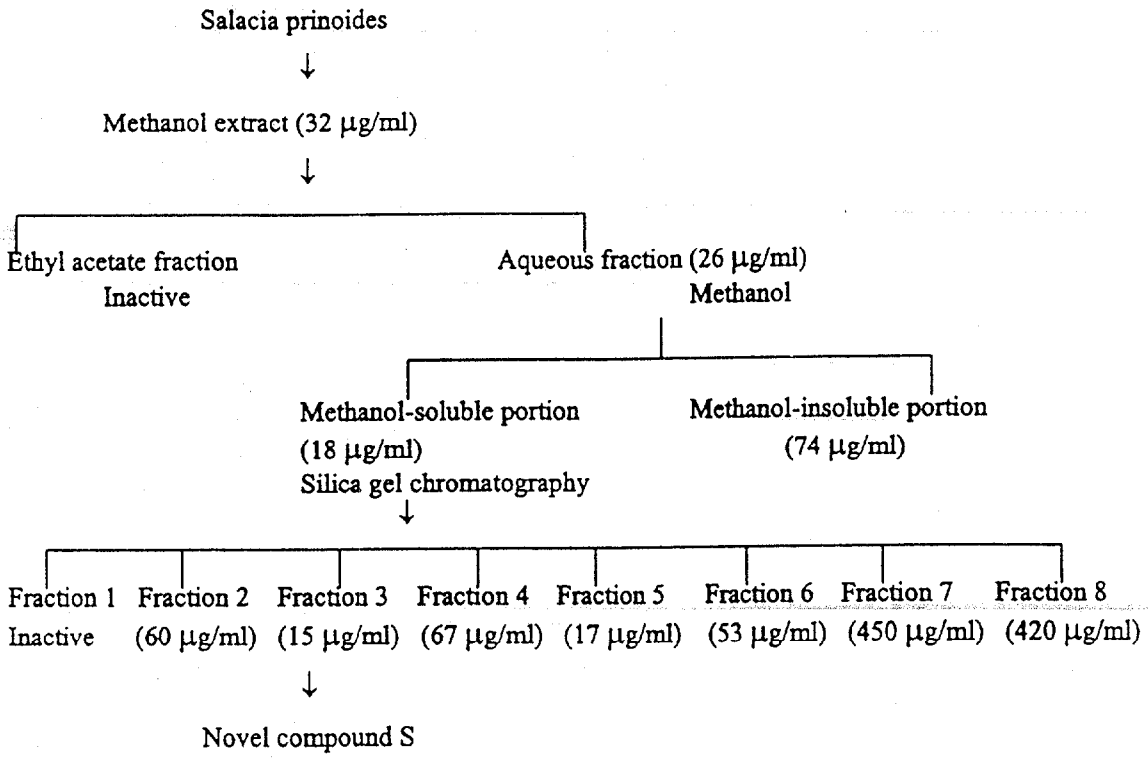
In the present invention, the novel compound SP expressed by the above Chemical Structural Formula can be prepared as a crystalline material. Accordingly, the powdered compound itself, or a mixture of the compound with some other appropriate excipient, milk sugar, starch, etc., can be formed into tablets, granules, etc. and used in this form.

Furthermore, the novel compound SP of the present invention can also be used as an additive which is added in very small amounts to gum or chocolate or to high-starch breads, noodles, confections, etc.

In addition, the novel compound SP of the present invention can be obtained by subjecting plants of the genus Salacia to an extraction using a desired medium. The thus obtained extract (including brew, steeping liquid or decoction) containing the novel compound SP can be used "as is", and such an extract can be also used after concentrating it into a concentrated liquid. Alternatively, the extract can be subjected to evaporative drying so as to be in a solid powder form. For example, the novel compound SP of the present invention can be used in the form of a liquid agent (such as an aqueous solution, etc.) as an antidiabetic agent or dieting agent.

Table 1

Fractionation Scheme and Sucrase Inhibiting Activity of Respective Fractions (IC_{50} values)



In the present invention, the above-described method for extracting and fractionating Salacia prinoides should be viewed as the optimal configuration from the standpoints of extraction efficiency and efficiency of removal of inactive portions, etc.

Various modifications are possible in the method used to extract and fractionate Salacia prinoides. For example, in the extraction process, some other solvent such as water or an alcohol other than methanol may be used instead of the methanol. Furthermore, in the process to remove inactive components (inactive component partition process), chloroform/water, for example, may be used instead of the partition process that uses ethyl acetate/water.

(4) Determination of Structure of Novel Compound S

The structure of the novel compound SP separated and purified as described above was determined.

More specifically, an empirical formula was determined by determining the composition of the novel compound SP by means of elemental analysis using an ordinary method, and the molecular formula was determined by separately measuring the molecular weight.

Next, X-ray diffraction was performed in order to determine the structural formula indicating the arrangement of the atomic bonds in the molecule.

In addition, specific rotation measurements, mass analysis and analysis of the infrared absorption spectrum (IR) and nuclear magnetic resonance spectrum (NMR) were also performed.

The results obtained are shown below. In the following description, the symbol A stands for "angstrom" (1×10^{-8} cm).

(i) Molecular formula: $C_9H_{18}S_2O_9$

(ii) Molecular weight: MW = 334.36

(iii) X-ray diffraction:

(iii-1) X-ray diffraction was performed under the following conditions:

X-ray diffraction apparatus:	AFC5R manufactured by Rigaku K.K.
Radiation:	MoKα (λ = 0.71069 A)
Temperature:	23°C
Attenuators:	Ni foil (factors: 3.6, 12.0, 42.0)
Take-off angle:	6.0°

(iii-2) The X-ray diffraction data (crystal data) was as follows:

Crystal color, habit:	colorless, prisms
Size of crystals (mm):	0.150 × 0.200 × 0.200
Crystallographic type:	monoclinic

Number of reflections used for unit cell determination
(2θ range, crystal reaction intensity): 25 (46.6 to 49.5°)

Omega scan peak width at half-height:0.36

Lattice parameters:	a = 6.433 (3) A
	b = 12.927 (2) A
	c = 8.372 (3) A
	β = 93.680 (3) A
	V = 694.800 (4) A^3
Space group:	P2 (#4)
Z-value:	2
Dm:	1.598 g/cm^3
F (000):	352
μ (MoKα):	4.05 cm^{-1}

The X-ray analysis diagram produced by the X-ray diffraction is shown in Figure 1.

Furthermore, a model diagram which makes the above-described X-ray analysis diagram in Figure 1 easier to comprehend in visual terms is shown in Figure 2.

In the present invention, structural analysis of the novel compound SP was also performed by means other than the X-ray analysis. Physical and chemical data for the novel compound SP obtained by these other analysis methods are shown below.

1. Measurement of specific rotation:

The measurement results obtained for specific rotation were as follows:

$[\alpha]_D^{28} = +4.9°$ (C = 0.35, MeOH)

2. Mass analysis:

The mass analysis results were as follows:

The analysis results obtained by high-resolution secondary ion mass analysis, i.e., high-resolution SIMS (m/z), were as follows:

(i) Calculated value: (note) $C_9H_{19}S_2O_9$ $(M + H)^+ = 335.0469$.

(ii) Experimental value: 335.0463.

3. Infrared absorption spectrum (IR) analysis:

The IR (KBr) analysis results were as follows:

IR (KBr): 3417 (-OH), 1261 and 1237 ($-OSO_3^-$), 1072 and 1018 (-CO-, -CS-), 801.

4. ^{1}H-NMR analysis:

The ^{1}H-NMR analysis results were as follows:

^{1}H-NMR (500 MHz, pyridine-d_5) : 4.31 (2H, br s, 2-H_2), 4.35, 4.58 (1H each, both dd, J=3.7, 11.6 Hz, 4′-H_2), 4.50(2H, m, 6-H_2), 4.60, 4.77 (1H each, both dd, J=4.6, 13.2Hz, 1′-H), 4.67(1H, dt, J=6.4, 6.7Hz, 5-H), 4.97(1H, m, 2′-H), 5.09(2H, br s, 2, 3-H), 5.24(1H, dt, J=3.7, 7.7Hz, 3′-H).

The spatial arrangement of H (hydrogen atoms) is shown in the X-ray analysis diagram (Figure 1).

5. ^{13}C-NMR analysis:

The ^{13}C-NMR analysis results were as follows:

^{13}C-NMR (125 MHz) : 50.5(2-C), 52.8(1′-C), 60.2(6-C), 62.3(4′-C), 67.6(2′-C), 72.5(5-C), 78.3(3-C), 79.2(3′-C), 79.3(2-C).

The spatial arrangement of C (carbon atoms) is shown in the X-ray analysis diagram (Figure 1).

According to the above structural analysis, the novel compound SP of the present invention has the above-described Chemical Structural Formula. Furthermore, as shown in Figures 1 and 2, the novel compound SP is an inner salt consisting of a 1-deoxy-4-thiorabinofuranosyl cation and a 1′-deoxyerythrosyl-3′-sulfate anion, which has a unique spiral-like configuration.

Next, characteristics and application examples of the novel compound SP of the present invention will be described below.

(i) Activity inhibiting effect on enzymes that break down glucides:

(i-1) Preparation of Enzymes

The brush border membrane obtained from the jejunum of male Wistar rats (body weight: 150 to 350 g) was used as a crude enzyme.

The brush border membrane was suspended in a 0.01 M maleic acid buffer solution (pH = 6.0), and this suspension was diluted to a concentration at which the substrate was hydrolyzed at the rate of approximately 25 to 50 n/mol/ml/minute.

The reason that the brush border membrane was selected as the crude enzyme is that this brush border membrane contains large amounts of α-glucosidase such as maltase, sucrase, isomaltase, etc.

(i-2) Test Method

For maltase, sucrase and isomaltase, 100 μL of various concentrations of the test drug was added to 50 μL of respective 74 mM maltose, sucrose and isomaltose (used as substrates), and the resulting preparations were pre-heated for 2 to 3 minutes at 37°C.

Next, 50 μL of the enzyme solution was added, and a reaction was performed for 30 minutes. The reaction was stopped by adding 800 μL of water, and placing the reaction mixture in a water bath at 92 to 97°C for 2 minutes.

The amount of glucose produced was measured by the glucose oxidase method (Glucose CII Test Wako).

In the above, the substrates and test drug were both dissolved in a maleic acid buffer solution (pH = 6.0) prior to use.

The results obtained are shown in Table 2 below.

Table 2 shows the inhibiting effects (inhibitory power: IC_{50} value) of the novel compound SP (product of the present invention) and Acarbose (conventional product) on maltase, sucrase and isomaltase (enzymes which break down disaccharides) originating in the small intestines of rats.

Table 2

Inhibiting Effects (IC_{50} values) of SP and Acarbose on Maltase, Sucrase and Isomaltase (enzymes which break down disaccharides) Originating in the Small Intestines of Rats.

Substrate	SP (product of the present invention)	Acarbose (conventional product)
Maltose (37 mM)	3.3	1.3
Sucrose (37 mM)	0.84	1.1
Isomaltose (3.7 mM)	0.51	100.0

(ii) Activity inhibiting effect on β-glucosidase:

This test was performed in order to demonstrate that the novel compound SP of the present invention has a specific activity for α-glucosidase only.

(ii-1) Preparation of Enzyme

β-glucosidase originating in almonds (manufactured by Sigma Co.) was dissolved in a 0.1 M acetic acid buffer solution (pH = 5.0), and this solution was diluted to a concentration at which the substrate was hydrolyzed at the rate of 5 n/mol/ml/minute.

(ii-2) Test Method

100 μL of the test drug was added to 50 μL of 10 mM p-nitrophenol-β-D-glycopyronoside (manufactured by Sigma Co.) used as a substrate, and this mixture was pre-heated for 5 minutes at 37°C.

Next, 50 μL of the enzyme solution was added, and a reaction was performed for 15 minutes. The reaction was stopped by adding 200 μL of a 0.2 M sodium carbonate solution.

The amount of p-nitrophenol produced was determined from the absorbance at 400 nm.

The substrate and test drug were both dissolved in a 0.1 M acetic acid buffer solution (pH = 5.0) prior to use.

As a result of the above test, it was ascertained that the novel compound SP of the present invention has no activity inhibiting effect on β-glucosidase.

(iii) Inhibiting effect on hyperglycemia in the case of sucrose loading:

The test drug was orally administered as an aqueous solution to fasting male Wistar rats (body weight: 130 to 170 g).

Next, after 30 minutes, sucrose was orally administered to the rats.

Then, 30 minutes after the administration of the sugar, 0.4 ml of blood was taken from the neck artery of each animal with the animals under restraint without anesthesia (during blood collection only). Following cooling with ice water, the blood serum was separated by centrifuging, and the glucose concentration (blood sugar level) was measured by the glucose oxidase method (Glucose CII Test Wako).

The above-described test was performed for the novel compound SP (product of the present invention) and Acarbose (conventional product).

The results obtained are shown in Table 3 below.

As shown in Table 3, the novel compound SP (product of the present invention) showed a stronger effect in inhibiting the elevation of blood sugar levels than Acarbose (conventional product) did.

Table 3

Effects of SP and Acarbose in Inhibiting Blood Sugar Elevation Caused by Sucrose Loading.

Compound name	Dosage mg/kg, po	Rate of inhibition of blood sugar elevation
Novel compound SP		30 minutes
(product of the present invention)	5	40.5±2.3
	10	62.1±3.8
	25	89.1±3.5
Acarbose	5	33.4±6.2
(conventional product)	10	48.5±6.9
	25	73.8±5.2

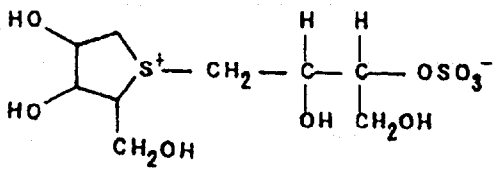
(iv) Dieting Effect

250 ml of a steeped liquid preparation (a brew) of Salacia prinoides (containing approximately 5 mg of the novel compound SP) was given to 10 persons suffering from obesity (average body weight: 72 kg) approximately 10 to 30 minutes before meals.

The above-described administration test was conducted for three months (90 days). As a result, an average weight loss of 5.5% (maximum weight loss: 15%) was observed. The loss of body weight was due mainly to a reduction in the amount of body fat and organ fat.

The above-described dieting effect was also similarly observed in steeped liquid preparations of Salacia oblonga and Salacia reticulata.

As seen from the above, the novel compound SP of the present invention, which is expressed by the Chemical Structural Formula:



and which is obtained by extraction and fractionation from Salacia prinoides and/or Salacia oblonga, has the characteristic of speifically inhibiting the activity of α-glucosidase (an enzyme which breaks down disaccharides, etc.) at intestinal levels. Accordingly, this compound can effectively inhibit the production of monosaccharides, which cause high blood sugar levels.

Furthermore, the novel compound SP of the present invention is a component that originates in a natural drug that has been used since ancient times. Accordingly, this compound is highly safe and shows a sufficient effect when administered at the rate of a few milligrams.

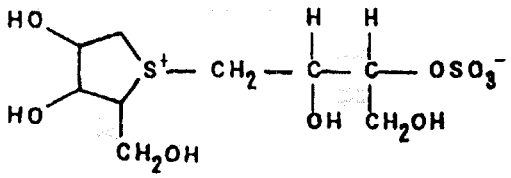
Thus, the novel compound SP of the present invention is extremely effective as a drug for inhibiting postprandial hyperglycemia, which is currently a major problem. In other words, this compound is extremely effective as an antidiabetic agent (i.e., an agent which combats diabetes mellitus).

Moreover, the novel compound SP of the present invention effectively inhibits the activity of α-glucosidase whch is an enzyme that breaks down glucides such as starch, and

oligosaccharides (disaccharides and trisaccharides). Accordingly, the breakdown of such glucides and oligosaccharides into monosaccharides is prevented, and the absorption of excess glucose in the body is prevented. As a result, by taking the compound of the present invention prior to meals, the absorption of glucose is inhibited, and postprandial hyperglycemia is eliminated. At the same time, necessary energy is obtained by the consumption of accumulated body fat and organ fat in the body. Thus, the compound has a dieting effect.

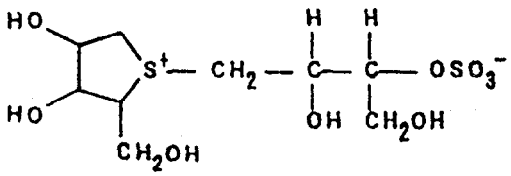
WHAT IS CLAIMED IS:

1. A compound expressed by chemical structural formula shown as:



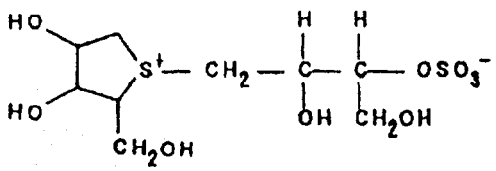
which is obtained from an extract of at least one of Salacia prinoides and Salacia oblonga belonging to the Celastaceae family.

2. An antidiabetic agent characterized in that said agent contains a compound having an α -glucosidase inhibiting effect and expressed by chemical structural formula shown as:



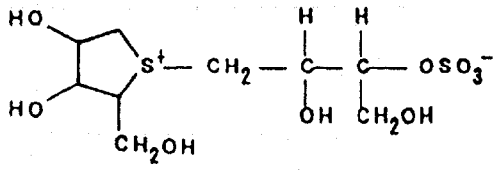
which is obtained from an extract of at least one of Salacia prinoides and Salacia oblonga belonging to the Celastaceae family.

3. A dieting agent characterized in that said agent contains a compound having an α-glucosidase inhibiting effect and expressed by chemical structural formula shown as:



which is obtained from an extract of at least one plant selected from the group consisting of Salacia prinoides, Salacia oblonga and Salacia reticulata which belong to the Celastaceae family.

4. A method for extracting a compound that has an α-glucosidase inhibiting effect and is expressed by chemical structural formula:



which is characterized in that said method comprising the steps of:

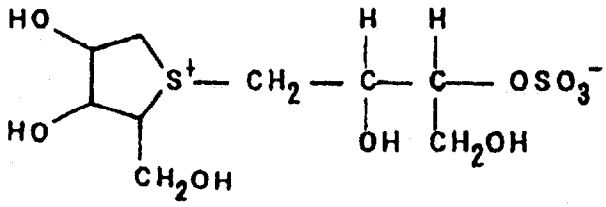
performing an extraction on Salacia prinoides belonging to the Celastaceae family by means of heated methanol, thus obtaining methanol extract,

performing a partition treatment on said methanol extract using ethyl acetate and water, and

performing a fractionation treatment by chromatography on a portion of said extract that has migrated into said water.

ABSTRACT OF THE DISCLOSURE

A compound expressed by chemical structural formula:



having the characteristic of specifically inhibiting the activity of α-glucosidase (an enzyme that breaks down disaccharides, etc.) at the intestinal level. The compound is obtained by extraction and fractionation from Salacia prinoides and/or Salacia oblonga, which are used as natural drugs. A highly safe antidiabetic agent and dieting agent are produced using the compound as a base.

FIG. 1

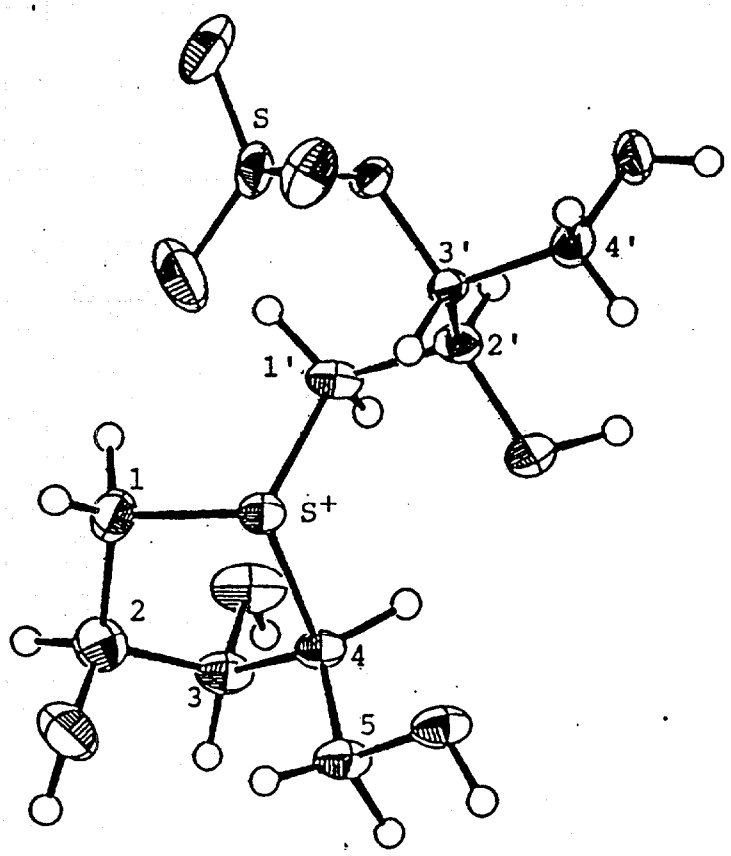
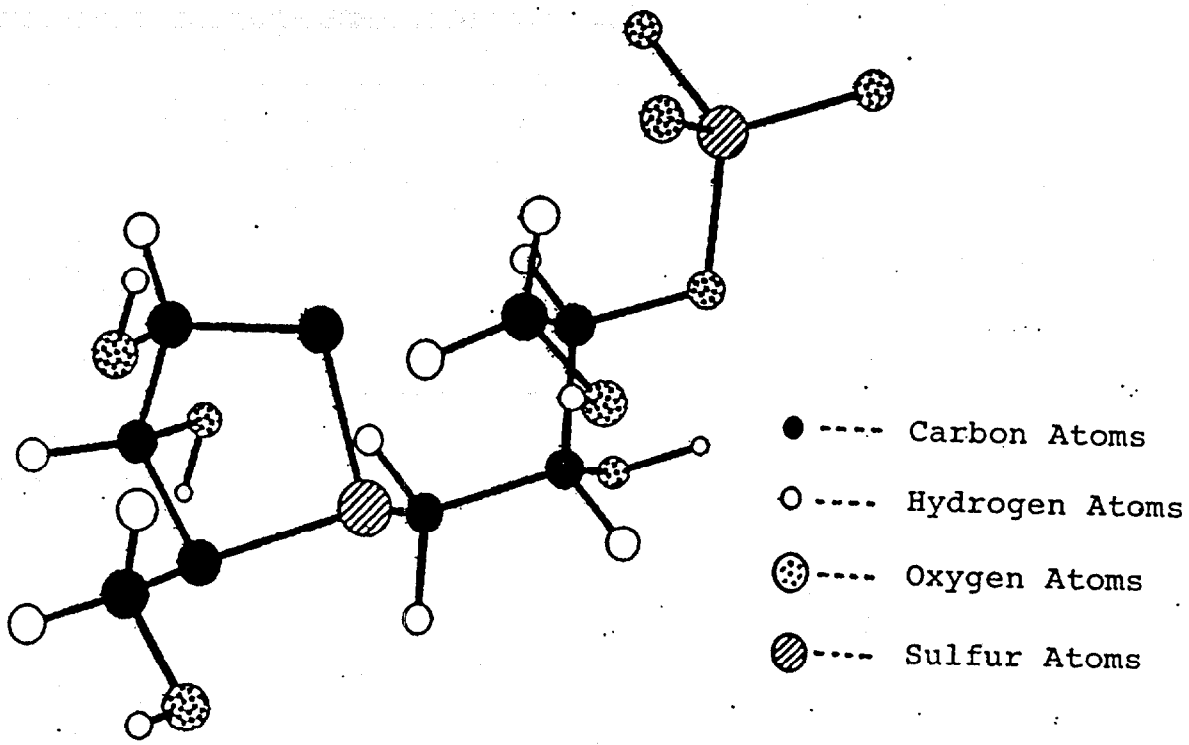


FIG. 2



English Translation from Japanese Information Magazine "AMUSE" published by Mainichi Shinbun in 1999.

Salacia Oblonga
– Inhibitory Effect on Sugar Discomposing Enzyme

There is a great attention on the plant, **Salacia**, which grows in Sri Lanka and Southern India, as it has been proven effective scientifically against increasing problem of life stage diseases like diabetes, hypertension as well as effective in lowering triglyceride and LDL cholesterol.

It had been used in Ayruvedic medicine with history of 4000 to 5000 years in India for diabetes, or as relief of the pain from neuropathy, rheumatism etc. Royal family or aristocrats had used it by brewing the stem or root of Salacia. From several years ago, it was brought into Japan. Dr. Joji Yamahara and Kyoto Medicine University group discovered first time in the world scientifically its blood sugar lowering effect, prohibitory effect on triglyceride formation, its active ingredient, toxicity test etc. Dr. Yamahara et al. proved by animal test by oral administration that the liquid brewed from Salacia showed selective inhibitory effect on sugar absorption toward those disaccharides (maltose and saccharose) at a rate of 80-100% and that it did not show effect on glucose.
This shows that extract of Salacia inhibits alpha glucositase, which is the sugar decomposing enzyme in intestine. Not only this, but it is found that it inhibits the action of aldose reductase, an enzyme which is activated at high blood situation. When the aldose reductase is activated, nervous interference, renal disturbance, cataract and so on occurs as well. Salacia has the effect of preventing those additional diseases derived from diabetes.

Currently, the population suffering from diabetes is increasing. WHO announces that those suffer from diabetes in the world count 135,000,000 while it would increase into 300,000,000 in 2025?
Those who have treatment at hospital only number 2,170,000 and all the others are not treated. Therefore, life style improvement is a real urge. As for Japanese, 95% accounts for Insulin non-dependent type and that half of

them are in obesity. There are medicines for diabetes, such as Insulin or Acarbose. However, they may produce side effects or low blood sugar situation. On the other hand, Salacia has no such side effects, or rather it has LDL cholesterol and triglyceride lowering effects as well as antioxidant action, which leads to a potentially big product with marketing concept of against diabetes and for weight loss diet. Besides, it produces more in intestines diasaccharide or trisaccharide, which become bait for lactobacillus. Lactobacillus would increase in number and improve intestinal flora. As a result, conditioning of intestine and preventive effect of colon cancer can be expected as secondary beneficial effect.

Dr. Yamahara, as mentioned earlier, studied more than 150 herbs in the world, Japan, China, South East Asia, Africa, S. America. After the careful screening, Salacia came out. Diabetes Report, which is published by WHO toward various medicine institution, introduces in its inaugural issue the function of Salacia as forefront of diabetes treatment, which shows how expectation toward Salacia is high for the prevention of life stage diseases.

Comparative study of Inhibitory effect on blood sugar increase between Gymnema Sylvestre and Salacia Oblonga

*Method of extraction

Add water 5 times more than the amount of each herb extract. After heating 2 hours, then filter and concentrate (less than 45℃) by lower pressure to eliminate solvent completely. Then the test extracts were obtained. Yield of Gymnema was 13.5%, while Salacia 8.0%.

*Testing Method of Inhibitory action against blood sugar increase

By administration of sugar. Blood samples were taken after 30 minutes.

*Results of examination

	Dose mg/kg, oral	Blood sugar level mg/dl
Normal Group		73.5+-2.5
Sugar Administered Group		142.8+-4.3
Salacia Oblonga Group	10	122.1+-5.2
	20	116.3+-2.0
	50	105.2+-5.4
	200	74.4+-4.5
Gymnema Sylvestre Group	500	146.8+-4.7
	1000	142.8+-4.3
	2000	139.9+-3.3

*Conclusion and Discussion

From the point of yield of Gymnema and Salacia, there was almost no effect observed against blood sugar increase when Gymnema was dosed 200 mg/kg. On the other hand, Salacia showed significant effect of inhibitory action against blood sugar increase from the dose of 10 mg.