

DESCRIPTION

Title of Invention: PRODUCTION METHOD FOR PENTOSAN POLYSULFATE

5 Technical Field

[0001]

The present invention relates to a method for producing pentosan polysulfate.

10 Background Art

[0002]

Heparin has been used as a therapeutic agent for thrombosis, osteoarthritis, and the like. However, since heparin is a substance separated from the organs of animals, such as
15 bovines or pigs, it is difficult to control the quality thereof. Further, there are cases where the use of heparin in treatment causes hesitation from the viewpoint of religious ethics etc. Therefore, the development of an alternative therapeutic agent that is free of animal-derived components, and that can be used
20 instead of heparin, has been desired.

[0003]

As such an alternative substance for heparin, pentosan polysulfate, for example, is known. Pentosan polysulfate is obtained by sulfating a plant-derived xylooligosaccharide. Since
25 such pentosan polysulfate is a substance free of animal-derived components, its use as an alternative therapeutic agent for heparin has been expected (for example, Patent Literature (PTL) 1 and Patent Literature (PTL) 2).

[0004]

30 PTL 1 and PTL 2 disclose a method for producing pentosan polysulfate, comprising sulfating xylan.

Xylans of hardwoods are known to have 5 to 7 acetyl groups per 10 xyloses at 2-position or 3-position under natural conditions (Non-patent Literature (NPL) 1). Patent Literature
35 (PTL) 3 discloses that pentosan polysulfate for pharmaceutical

use contains a xylose unit that binds to uronic acid at 4-position, and that is acetylated at 3-position.

Citation List

5 Patent Literature

[0005]

PTL 1: WO2010/000013

PTL 2: JPS48-043100A

PTL 3: WO2014/114723

10 Non-patent Literature

[0006]

NPL-1: CMC Publishing Co., Ltd., "*Wood Chemicals no Gijyutsu* (Techniques of Wood Chemicals)," First Edition 2007, p. 108

15 Summary of Invention

Technical Problem

[0007]

20 An object of the present invention is to provide an inexpensive and efficient production method as a method for producing pentosan polysulfate.

Solution to Problem

[0008]

25 As a result of intensive studies to solve the above problem, the present inventors have found that when a method for producing pentosan polysulfate includes a step of depolymerizing a plant-derived raw material and a sulfation step in this order, the efficiency of the method for producing pentosan polysulfate can be significantly improved. The inventors further found that
30 when the method includes a deacetylation step after the depolymerization step, pentosan polysulfate can be produced with a higher yield than the yield achieved by a method that does not include a deacetylation step.

35 Specifically, the present invention has the following constitution.

[0009]

[1] A method for producing pentosan polysulfate, comprising
a first step of obtaining an acidic xylooligosaccharide
from a plant-derived raw material; and

5 a second step of obtaining pentosan polysulfate from
the acidic xylooligosaccharide,

the first step comprising a step of depolymerizing the
plant-derived raw material,

the second step comprising a step of sulfating the
10 acidic xylooligosaccharide; and

the method comprising a deacetylation step of adding a
base to achieve a pH of 11 or higher, the deacetylation step
being a step performed after the depolymerization step.

[2] The method for producing pentosan polysulfate according to
15 [1], wherein the deacetylation step comprises stirring a solution
containing the acidic xylooligosaccharide at a pH of 11 or higher
for 1 hour or more.

[3] The method for producing pentosan polysulfate according to
[1], wherein the deacetylation step comprises stirring a solution
20 containing the acidic xylooligosaccharide at a pH of 12 or higher
for 0.5 hours or more.

[4] The method for producing pentosan polysulfate according to
any one of [1] to [3], wherein the base is sodium hydroxide.

[5] The method for producing pentosan polysulfate according to
25 any one of [1] to [4], wherein the depolymerization step is
performed under non-alkaline conditions.

[6] The method for producing pentosan polysulfate according to
any one of [1] to [5], wherein the depolymerization step is a
heat treatment step.

30 [0010]

[7] The method for producing pentosan polysulfate according to
[6], wherein the heat treatment step is a step of heating to
120°C or higher under non-alkaline conditions.

[8] The method for producing pentosan polysulfate according to
35 any one of [1] to [7], wherein the plant-derived raw material is

a wood-derived raw material.

[9] The method for producing pentosan polysulfate according to any one of [1] to [8], further comprising a molecular weight adjustment step between the first step and the second step.

5 [10] The method for producing pentosan polysulfate according to [9], further comprising a post-molecular-weight-adjustment separation and purification step performed after the molecular weight adjustment step.

10 [11] The method for producing pentosan polysulfate according to any one of [1] to [10], wherein the second step further comprises a post-sulfation purification step performed after the sulfation step.

[12] The method for producing pentosan polysulfate according to [11], wherein the second step further comprises a powdering step
15 performed after the post-sulfation purification step.

[13] A pentosan polysulfate produced by the method according to any one of [1] to [12].

[14] The pentosan polysulfate according to [13], which has an acetyl group content of 0 to 2.0 mass%.

20 [15] An anticoagulant comprising the pentosan polysulfate according to [13] or [14].

Advantageous Effects of Invention

[0011]

25 The present invention provides a method for producing pentosan polysulfate having a low acetyl group content. The production method of the present invention can efficiently produce pentosan polysulfate with a high yield.

30 Brief Description of Drawings

[0012]

Fig. 1 is a diagram illustrating a process of producing pentosan polysulfate.

Fig. 2 is a diagram illustrating a process of producing
35 pentosan polysulfate.

Fig. 3 is a graph showing anti-IIa activity and anti-Xa activity of pentosan polysulfates with different acetyl group contents obtained in the Examples and Comparative Examples.

5 Description of Embodiments

[0013]

The present invention is described below in detail. The constituent features may be described below based on typical embodiments and specific examples; however, the present invention
10 is not limited to these embodiments.

[0014]

Method for Producing Pentosan Polysulfate

The present invention relates to a method for producing pentosan polysulfate derived from an acidic xylooligosaccharide.

15 The present invention relates to a method for producing pentosan polysulfate, which comprises a first step of obtaining an acidic xylooligosaccharide from a plant-derived raw material, and a second step of obtaining pentosan polysulfate from the acidic xylooligosaccharide, the method further comprising a
20 deacetylation step. Since the production method of the present invention comprises a step of depolymerizing a plant-derived raw material and a sulfation step in this order, pentosan polysulfate can be efficiently produced. Since the production method of the present invention further comprises a deacetylation step,
25 pentosan polysulfate can be produced with a high yield.

[0015]

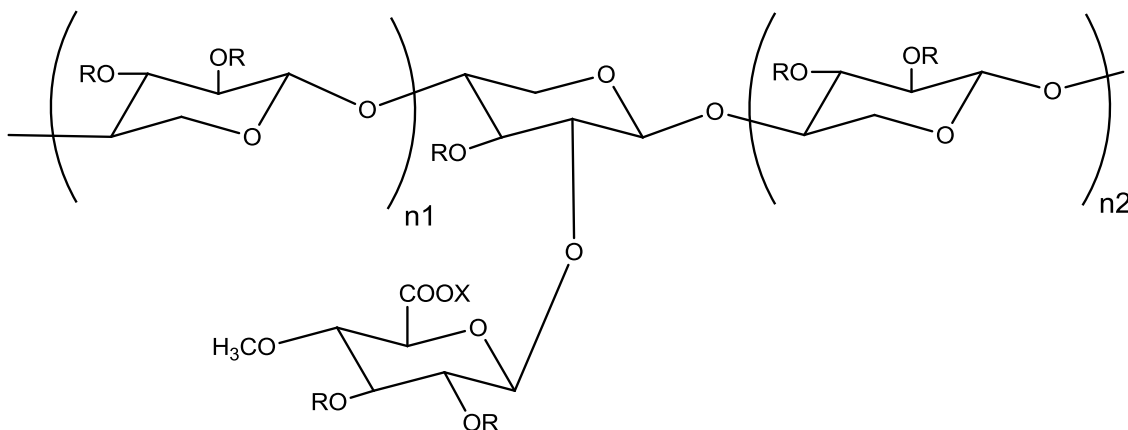
Pentosan polysulfate is a compound obtained by sulfating at least one hydroxyl group of xylooligosaccharide. The pentosan polysulfate as referred to herein includes salts of
30 pentosan polysulfate, solvates of pentosan polysulfate, and solvates of salts of pentosan polysulfate. More specifically, the production method according to the present invention includes a method for producing a salt of pentosan polysulfate, a solvate of pentosan polysulfate, or a solvate of a salt of pentosan
35 polysulfate. The salt of pentosan polysulfate is preferably a

pharmaceutically acceptable salt. Examples include pentosan polysulfate sodium, pentosan polysulfate potassium, pentosan polysulfate calcium, and the like. The solvate is preferably a pharmaceutically acceptable solvate. Examples of solvents include water.

[0016]

Pentosan polysulfate derived from an acidic xylooligosaccharide contains a structure represented by the following formula. The pentosan polysulfate may contain one structure represented by the following formula, or may contain two or more structures represented by the following formula. When the pentosan polysulfate contains two or more structures represented by the following formula, the following structure shows a repeating unit of pentosan polysulfate.

[0017]



[0018]

In the above formula, each R independently represents a hydrogen atom, $-\text{COCH}_3$, or $-\text{SO}_3\text{X}^1$; and at least one R is $-\text{SO}_3\text{X}^1$. X^1 is a hydrogen atom or a monovalent or divalent metal; preferably a hydrogen atom, sodium, potassium, or calcium; more preferably sodium, potassium, or calcium; and particularly preferably sodium. X represents a hydrogen atom or a monovalent or divalent metal; preferably sodium, potassium, or calcium; and particularly preferably sodium. n_1 and n_2 each independently represent an integer of 0 or more and 30 or less, and at least one of n_1 and n_2 is an integer of 1 or more.

[0019]

In the above formula, $n_1 + n_2$ is preferably 1 to 27, more preferably 2 to 18, and even more preferably 3 to 10.

[0020]

5 In the above formula, X is preferably a monovalent or divalent metal, and is more preferably a pharmaceutically acceptable salt of pentosan polysulfate. For example, X is preferably sodium, potassium, or calcium. In such a case, the salt of pentosan polysulfate is pentosan polysulfate sodium,
10 pentosan polysulfate potassium, or pentosan polysulfate calcium. Among these, it is particularly preferable that the salt of pentosan polysulfate is pentosan polysulfate sodium.

[0021]

The pentosan polysulfate may contain one structure
15 represented by the above formula, or may contain two or more structures represented by the above formula. When the pentosan polysulfate contains two or more structures represented by the above formula, the above structure shows a repeating unit of pentosan polysulfate.

20 The portion that is an end of the structure represented by the above formula and that does not bind to a structure represented by the above formula may be -OR. That is, -OR may bind to the left terminus (n_1 side) of the above formula, whereas -R may bind to the right terminus (n_2 side) of the above formula.

25 [0022]

In the present invention, pentosan polysulfate can be obtained by sulfating an acidic xylooligosaccharide. The acidic xylooligosaccharide, which is one of the xylooligosaccharides, contains at least one uronic acid bound to at least one of the
30 xylose units in a xylooligosaccharide molecule. That is, the acidic xylooligosaccharide has, as a side chain, at least one uronic acid residue per xylooligosaccharide molecule. The average number of uronic acid residues per molecule of acidic xylooligosaccharide is preferably 1 or more and 3 or less, more
35 preferably 1 or more and 2 or less. The average number of uronic

acid residues per molecule of acidic xylooligosaccharide can be measured by the carbazole-sulfuric acid method, or the colorimetric method using sodium tetraborate.

[0023]

5 Based on the disclosure of WO2014/114723 and "*Wood Chemicals no Gijyutsu* (Techniques of Wood Chemicals)" (CMC Publishing Co., Ltd.) referred to above, it is assumed that known pentosan polysulfates include a certain amount of xylose units to which acetyl groups ($-\text{COCH}_3$), as well as uronic acid residue(s),
10 bind. The pentosan polysulfate obtained by the production method of the present invention has a lower acetyl group content; in particular, the pentosan polysulfate has a lower content of acetyl groups binding to specific xylose units, as described above.

15 [0024]

More specifically, the pentosan polysulfate obtained by the production method of the present invention has an acetyl group content of 0 to 2.0% by mass. The pentosan polysulfate preferably has an acetyl group content of 0 to 1.0 mass%, more
20 preferably 0 to 0.4 mass%, and even more preferably 0 to 0.3 mass%. It is particularly preferable that the acetyl group content of pentosan polysulfate is substantially 0 mass%. That is, it is particularly preferable that the pentosan polysulfate obtained by the production method of the present invention does
25 not include pentosan polysulfate of the above formula wherein R is $-\text{COCH}_3$.

[0025]

The acetyl group content of polysulfate pentosan can be calculated from the integral ratio of peaks in ^1H -NMR measurement,
30 as described in the Examples. More specifically, first, ^1H -NMR measurement is performed using a ^1H -NMR measurement solution containing a specific amount of pentosan polysulfate and a specific amount of an internal standard substance. By comparing the peak of a specific group of the internal standard substance
35 and the peak of acetyl group in the obtained spectrum to obtain

an integral ratio of the acetyl peak to the specific group, the molar amount of acetyl groups in the solution is obtained. The molar amount of acetyl groups is then multiplied by 43; and the obtained value is divided by the average molecular weight
5 obtained separately, so as to obtain the mass% of acetyl groups.
[0026]

Plant-Derived Raw Material

In the present invention, acidic xylooligosaccharide can be obtained by depolymerizing a plant-derived raw material.
10 Examples of plant-derived raw materials include wood-derived raw materials, seed-derived raw materials, grain-derived raw materials, fruit-derived raw materials, and the like. Examples of plant-derived raw materials further include cottons such as cotton linter and cotton lint; herbaceous plants such as kenaf,
15 hemp, ramie, and rice straw; and the like. Such raw materials derived from various sources may be used in combination as the plant-derived raw material.
[0027]

Among these, wood-derived raw materials are
20 particularly preferable as the plant-derived raw material. Examples of wood-derived raw materials include wood materials such as softwoods and hardwoods. The wood-derived raw material is preferably at least one selected from softwoods and hardwoods; and hardwoods are more preferable. The wood-derived raw material
25 may be a mixture of softwood and hardwood. A bark may also be used as the wood-derived raw material.
[0028]

Examples of hardwoods include beech, *Eucalyptus globulus*, *Eucalyptus grandis*, *Eucalyptus urograndis*, *Eucalyptus*
30 *pellita*, *Eucalyptus brachiana*, *Acacia mearnsii*, and the like. Examples of softwoods include Japanese cedar, Japanese cypress, pine, hiba, Japanese hemlock, and the like.
[0029]

The wood-derived raw material preferably has a volume
35 weight of 450 kg/m³ or more and 700 kg/m³ or less, and more

preferably 500 kg/m³ or more and 650 kg/m³ or less. When the wood-derived raw material has a volume weight within the above-mentioned range, the efficiency of producing acidic xylooligosaccharide can be enhanced.

5 [0030]

The wood-derived raw material is preferably wood chips obtained by crushing one or more of the above-mentioned woods. When wood chips are used as a plant-derived raw material, depolymerization of the plant-derived raw material can efficiently proceed, and the efficiency of producing acidic xylooligosaccharide can be enhanced.

[0031]

First Step

Depolymerization Step

15 The method for producing pentosan polysulfate of the present invention comprises a first step of obtaining an acidic xylooligosaccharide from a plant-derived raw material, as shown in Fig. 1. In the method for producing pentosan polysulfate of the present invention, the first step comprises a step of
20 depolymerizing a plant-derived raw material. In the step of depolymerizing a plant-derived raw material, the plant-derived raw material is chemically and/or physically decomposed to produce an acidic xylooligosaccharide. Examples of the chemical and/or physical decomposition step include a heat treatment step,
25 an alkali treatment step, an acid treatment step, an enzyme treatment step, an ionic liquid treatment step, a catalytic treatment step, and the like. Among these steps, the depolymerization step is preferably at least one selected from a heat treatment step and an enzyme treatment step; and is more
30 preferably a heat treatment step. The heat treatment step may be a heating and pressurizing step.

The depolymerization step is preferably performed under non-alkaline conditions (herein referred to as pH 9 or less, preferably pH 8 or less, and more preferably pH 7 or less).

35 [0032]

The heat treatment step is a step of heating a plant-derived raw material in the presence of a solution. Since the plant-derived raw material is hydrolyzed in such a heat treatment step, the heat treatment step is sometimes referred to as a
5 hydrolysis treatment step or a pre-hydrolysis treatment step. The solution used in the heat treatment step is preferably water. The ratio (mass ratio) of water to the plant-derived raw material is preferably in the range of 1:1 to 1:10. When the ratio of water to the plant-derived raw material is set within the above range,
10 the hydrolysis reaction can proceed efficiently. The water used in the heat treatment step may be water added separately from the plant-derived raw material; or a part of the water used in the heat treatment step may be water originally contained in the plant-derived raw material.

15 [0033]

In the heat treatment step, in addition to the plant-derived raw material and water, other chemicals may also be added. Examples of such other chemicals include alkalis, acids, and chelating agents. Chemicals that directly or indirectly
20 assist the depolymerization of polysaccharides, such as scale inhibitors, pitch control agents, and ionic liquid, may also be added.

[0034]

The heat treatment step is a step of heating a plant-derived raw material in the presence of water. The heating
25 temperature (liquid temperature) in this step is preferably 30°C or higher, more preferably 50°C or higher, even more preferably 75°C or higher, still even more preferably 90°C or higher, particularly preferably 100°C or higher, and most preferably
30 120°C or higher. On the other hand, the heating temperature (liquid temperature) is preferably 300°C or lower, more preferably 250°C or lower, and even more preferably 200°C or lower.

[0035]

35 The treatment time in the heat treatment step can be

determined, as appropriate, according to the treatment temperature. The treatment time is, for example, preferably 5 minutes or more, more preferably 10 minutes or more, and even more preferably 20 minutes or more. The P factor expressed by the following formula is a product of temperature and time in the heating treatment. It is preferable to adjust the P factor within a preferred range.

[0036]

$$P = \int_{t_0}^t \frac{k_{H1(T)}}{k_{100^{\circ}\text{C}}} \cdot dt = \int_{t_0}^t \text{Exp} \cdot \left(40.48 - \frac{15106}{T} \right) \cdot dt$$

[0037]

In the above formula, P represents P factor, T represents absolute temperature ($^{\circ}\text{C} + 273.5$), t represents heat treatment time, and $k_{H1(T)}/k_{100^{\circ}\text{C}}$ represents the relative rate of hydrolysis of glycosidic bonds.

[0038]

In the heat treatment step, the P factor is preferably set at 200 or more, more preferably 250 or more, and even more preferably 300 or more. On the other hand, the P factor is preferably 1000 or less. In the heat treatment step, the P factor is adjusted as appropriate so that the average degree of polymerization of acidic xylooligosaccharide can be within a desired range, and the molecular weight of the obtained pentosan polysulfate can be thereby adjusted.

[0039]

In the heat treatment step, the solution containing a plant-derived raw material preferably has a pH of 9 or less, more preferably a pH of 8 or less, and even more preferably a pH of 7 or less. That is, the heat treatment step is preferably performed under non-alkaline conditions. The pH value described above refers to the pH of the solution before the heat treatment.

[0040]

In the heat treatment step, a raw material-derived acid may be dissociated, and acid hydrolysis may proceed at least partially. Examples of plant raw material-derived acids include organic acids, such as acetic acid and formic acid. In this case,
5 the solution containing a plant-derived raw material has a further reduced pH after the acid hydrolysis.
[0041]

The method for producing pentosan polysulfate preferably comprises a heat treatment step as the first step.
10 This step can enhance the efficiency of producing acidic xylooligosaccharide, and thus lead to increased efficiency of producing pentosan polysulfate. When the method includes a heat treatment step as the first step, the production method can significantly reduce the number of steps required to produce
15 acidic xylooligosaccharide, as compared with the conventional methods. When the method includes a heat treatment under non-alkaline conditions as the first step, the production method can efficiently produce acidic xylooligosaccharide with suppressed coloration because the acidic xylooligosaccharide is not
20 substituted with hexenuronic acid.
[0042]

In the present invention, the depolymerization step is preferably a heat treatment step; however, it may be a step other than the heat treatment step. For example, when the
25 depolymerization step is an enzyme treatment step, the depolymerization step comprises a step of mixing a plant-derived raw material with an enzyme. Examples of usable enzymes include hemicellulase and the like. Specific examples include commercially available enzyme preparations, such as Cellulosin
30 HC100 (trade name, manufactured by HBI Enzymes Inc.), Cellulosin TP25 (trade name, manufactured by HBI Enzymes Inc.), Cellulosin HC (trade name, manufactured by HBI Enzymes Inc.), Cartazyme (trade name, manufactured by Clariant AG), Ecopulp (trade name, manufactured by Rohm Enzyme GmbH), Sumizyme (trade name,
35 manufactured by Shin Nihon Chemicals Corporation), Pulpzyme

(manufactured by Novo Nordisk), and Multifect 720 (Genencor); and xylanase produced by microorganisms belonging to genus *Trichoderma*, genus *Thermomyces*, genus *Aureobasidium*, genus *Streptomyces*, genus *Aspergillus*, genus *Clostridium*, genus *Bacillus*, genus *Thermotoga*, genus *Thermoascus*, genus *Cardoceram*, genus *Thermomonospora*, or the like.

[0043]

In the enzyme treatment step, an enzyme is added to a solution obtained by mixing a plant-derived raw material with water. The temperature of the solution during this addition is preferably 10°C or higher and 90°C or lower, and more preferably 30°C or higher and 60°C or lower. The temperature of the solution is preferably a temperature close to the optimal temperature of the enzyme used. The pH of the solution is also preferably adjusted to a range in which the activity of the enzyme is enhanced. For example, the pH of the solution is preferably adjusted to a pH of 3 or more and 10 or less.

[0044]

When the depolymerization step is an alkali treatment step or an acid treatment step, the depolymerization step comprises a step of mixing a plant-derived raw material with an alkaline solution or an acid solution. In the alkali treatment step, sodium hydroxide or potassium hydroxide is preferably added. In the acid treatment step, hydrochloric acid, sulfuric acid, acetic acid, or the like is preferably added. In the above cases as well, heating or pressurization may be performed as appropriate.

[0045]

When the depolymerization step is at least one selected from an enzyme treatment step, an alkali treatment step, and an acid treatment step, the production method may further comprise, after the treatment step, a squeezing step, an extraction step, a heating step, a filtration step, a separation step, a purification step, a concentration step, a desalting step, or the like. Further, the method may comprise a molecular weight

reduction step after the treatment step. Examples of other steps include the steps described in JP2003-183303A, the contents of which are incorporated herein by reference.

[0046]

5 Filtration Step

In the method for producing pentosan polysulfate of the present invention, the first step may further comprise a filtration step after the depolymerization step described above. In the filtration step, the reaction mixture is separated into
10 solids of the plant-derived raw material, and a solution other than the solids. More specifically, when a filtration step is provided after the depolymerization step, the reaction product is separated into solids, which are used as a pulp raw material, and a filtrate. The solids used as a pulp raw material are subjected
15 to a digestion step or the like as a post-step, to thereby provide a cellulose raw material (dissolving pulp).

[0047]

The collected filtrate can be separated into a gas layer and a liquid layer. Since the gas layer contains a large
20 amount of furfurals, these furfurals can be recovered from the gas layer to isolate furfurals. On the other hand, the liquid layer contains a large amount of hemicellulose including acidic xylooligosaccharide and neutral xylooligosaccharide. The acidic xylooligosaccharide contained in the liquid layer can be
25 separated and purified in the step described below.

[0048]

Separation and Purification Step

In the method for producing pentosan polysulfate, the first step may further comprise a separation and purification
30 step that is performed after the depolymerization step. When the first step comprises the filtration step described above, a separation and purification step is preferably provided after the filtration step.

Fig. 2 shows a flow chart in which a filtration step is
35 provided after the depolymerization step, and a separation and

purification step is provided after the filtration step. The first step may include a separation and purification step performed immediately after the depolymerization step.

Preferably, however, a filtration step is provided after the

5 depolymerization step, and a step of separating acidic xylooligosaccharide from the obtained filtrate and purifying the acidic xylooligosaccharide is provided. The filtration step may be provided as a part of the separation and purification step; or
10 purification step, as shown in Fig. 2. The separation and purification step is a step of separating and purifying acidic xylooligosaccharide. Since the filtrate obtained in the filtration step contains various saccharides, such as neutral xylooligosaccharide, in addition to acidic xylooligosaccharide,
15 the separation and purification step is also a step of removing such xylooligosaccharides other than acidic xylooligosaccharide.
[0049]

In the separation and purification step, for example, ion exchange chromatography, affinity chromatography, gel

20 filtration, ion exchange treatment, NF membrane treatment, UF membrane treatment, RO membrane treatment, activated carbon treatment, or like methods are preferably used. In the separation and purification step, it is also preferable to perform the above methods in combination. In particular, when ion exchange
25 chromatography is performed in the separation and purification step, acidic xylooligosaccharide can be selectively separated and purified. In ion exchange chromatography, acidic xylooligosaccharide is adsorbed to thereby mainly obtain acidic xylooligosaccharide from the sugar liquid (filtrate).

30 Specifically, sugar liquid is first treated with a strong cation exchange resin to remove metal ions from the sugar liquid.

Subsequently, using a strong anion exchange resin, sulfate ions or the like are removed from the sugar liquid. The resulting sugar liquid is treated with a weak anion exchange resin to

35 adsorb acidic xylooligosaccharide on the resin. The acidic

oligosaccharide adsorbed on the resin is eluted with a low-concentration salt (NaCl, CaCl₂, KCl, MgCl₂, etc.) to thereby obtain an acidic xylooligosaccharide solution containing a small amount of impurities.

5 [0050]

Concentration Step

In the method for producing pentosan polysulfate of the present invention, the first step may further comprise a concentration step. The concentration step is preferably provided, for example, after the filtration step and before the separation and purification step, as shown in Fig. 2. When the first step includes a concentration step, the separation and purification step can be more efficiently performed, and the efficiency of producing pentosan polysulfate can be enhanced.

15 [0051]

Examples of the concentration step include a membrane treatment step using an NF membrane, an ultrafiltration membrane, a reverse osmosis membrane, or the like; a concentration step using evaporation etc.; and the like.

20 [0052]

In the concentration step, the solution is preferably concentrated, so that the resulting concentrate has an acidic xylooligosaccharide content of 10% or more and 80% or less, and more preferably 20% or more and 60% or less, based on the total mass of the concentrate.

25 [0053]

Dehydration Step

In the first step, the acidic xylooligosaccharide may be obtained in the form of an acidic xylooligosaccharide solution; or may be subjected to a dehydration step, and obtained in the form of an acidic xylooligosaccharide concentrate or an acidic xylooligosaccharide powder. When acidic xylooligosaccharide powder is to be produced, the production method preferably further comprises a powdering step after the separation and purification step. In the present invention, when

35

the method includes a dehydration step, sulfation in the sulfation step described below can proceed efficiently.

[0054]

In the powdering step, the acidic xylooligosaccharide
5 solution obtained in the separation and purification step is treated using, for example, a spray dryer, a freeze-drying machine, a hot-air drying machine, or a water-soluble organic solvent, to thereby obtain an acidic xylooligosaccharide powder.

[0055]

10 Second Step

Sulfation Step

As shown in Fig. 1, the method for producing pentosan polysulfate of the present invention includes a first step and a second step, wherein the acidic xylooligosaccharide obtained in
15 the first step is sulfated in the second step to thereby obtain pentosan polysulfate. That is, the second step includes a sulfation step.

[0056]

The average degree of polymerization of acidic
20 xylooligosaccharide to be subjected to sulfation is preferably adjusted, as appropriate, according to the molecular weight of pentosan polysulfate to be obtained as a final product.

[0057]

The average degree of polymerization of acidic
25 xylooligosaccharide can be calculated by dividing the total sugar amount of the acidic xylooligosaccharide by the amount of reducing sugar. In calculation of the total sugar amount, first, an acidic xylooligosaccharide solution is maintained at 50°C and centrifuged at 15000 rpm for 15 minutes. The total sugar amount
30 of the supernatant is then quantified by the phenol-sulfuric acid method ("*Kangento no Teiryo-Ho* (Method of Quantifying Reducing Sugar)"; published by Gakkai Shuppan Center). The calibration curve to be used in this quantification is produced using D-xylose (Wako Pure Chemical Industries, Ltd.). The amount of
35 reducing sugar is quantified by the Somogyi-Nelson method

("Kangento no Teiryo-Ho (Method of Quantifying Reducing Sugar)"; published by Gakkai Shuppan Center). The calibration curve to be used in this quantification is also produced using D-xylose (Wako Pure Chemical Industries, Ltd.).

5 [0058]

In the sulfation step, sulfuric acid or a sulfuric acid derivative is added to an acidic xylooligosaccharide solution to sulfate acidic xylooligosaccharide. Examples of sulfuric acid derivatives include sulfur trioxide pyridine complex,
10 chlorosulfonic acid, and the like. In this step, the concentration of the acidic xylooligosaccharide solution is preferably 0.1 mass% or more and 20 mass% or less. Sulfuric acid is preferably added to a concentration of 0.1 mass% or more and 50 mass% or less to the acidic xylooligosaccharide solution of
15 the above-mentioned concentration. After the addition of sulfuric acid, the acidic xylooligosaccharide solution preferably has a pH of 1 or more and 9 or less.

[0059]

Post-Sulfation Purification Step

20 In the method for producing pentosan polysulfate of the present invention, the second step may further comprise a post-sulfation purification step after the sulfation. When the method includes such a post-sulfation purification step, a high-purity pentosan polysulfate can be obtained.

25 [0060]

In the post-sulfation purification step, a method such as centrifugation, membrane filtration, dialysis, water-soluble organic solvent treatment, or activated carbon treatment is preferably used. Among these, water-soluble organic solvent
30 treatment and activated carbon treatment can selectively separate and purify sulfonated pentosan polysulfate, and are therefore preferably used.

[0061]

Powdering Step

35 In the second step, sulfated pentosan polysulfate may

be obtained in the form of a pentosan polysulfate solution; or may be subjected to a powdering step, and obtained in the form of a pentosan polysulfate powder. When pentosan polysulfate powder is to be produced, the production method preferably further
5 comprises a powdering step after the post-sulfation purification step.

[0062]

As the powdering step, for example, the pentosan polysulfate solution obtained in the post-sulfation purification
10 step can be treated using a spray dryer, a freeze-drying machine, a hot-air drying machine, a water-soluble organic solvent, or the like, to thereby obtain a pentosan polysulfate powder.

[0063]

Pentosan polysulfate is obtained by subjecting acidic
15 xylooligosaccharide to the second step described above. The pentosan polysulfate thus obtained preferably has a sulfur content of 10 mass% or more and 20 mass% or less, based on the total mass of the pentosan polysulfate. The sulfur content of pentosan polysulfate can be determined by the oxygen flask
20 combustion method described in General Tests of the Japanese Pharmacopoeia.

[0064]

Deacetylation Step

The method for producing pentosan polysulfate of the
25 present invention comprises a deacetylation step that is performed at any stage after the depolymerization step. The deacetylation step is a step for reducing the acetyl group content of pentosan polysulfate. More specifically, the deacetylation step is a step of adding a base to adjust the pH of
30 a solution containing a substance obtained from a plant-derived raw material, such as acidic xylooligosaccharide (herein also referred to as a "solution containing acidic xylooligosaccharide or the like"), to pH 11 or more. In the deacetylation step, for example, the solution obtained after the depolymerization, the
35 filtrate obtained by the filtration step, the solution containing

acidic xylooligosaccharide after the separation and purification step and before the sulfation step, or the solution containing acidic xylooligosaccharide after the sulfation step (pentosan polysulfate) may be adjusted to a pH of 11 or higher. When the
5 solution containing acidic xylooligosaccharide after the separation and purification step and before the sulfation step is adjusted to a pH of 11 or higher, a pentosan polysulfate of stable quality, having a reduced acetyl group content, can be obtained; and sites to which acetyl groups have been bonded can
10 also be sulfated, thereby enhancing the sulfation efficiency and thus leading to increased efficiency of producing pentosan polysulfate. When the solution containing acidic xylooligosaccharide after the sulfation step (pentosan polysulfate) is adjusted to a pH of 11 or higher, the
15 purification step can be performed more efficiently. The solution containing acidic xylooligosaccharide or the like is preferably an aqueous solution. The solution containing acidic xylooligosaccharide may herein also be referred to as the acidic xylooligosaccharide solution.

20 [0065]

The pH in the deacetylation step is preferably pH 11 to 14, and more preferably pH 12 to 13. The solution subjected to the deacetylation step is preferably maintained at pH 11 or higher for 0.5 hours or more, more preferably at pH 11 or higher
25 for 1.0 hour or more, even more preferably at pH 11 or higher for 2.0 hours or more, and particularly preferably at pH 11 or higher for 3.0 hours or more. In particular, when the pH is lower than 12, the solution is preferably maintained for 1.0 hour or more. Particularly preferred conditions can be, for example, conditions
30 such that the solution is maintained at pH 12 to 13 for 3 hours or more.

[0066]

While the solution is maintained in the pH range described above, the solution is preferably stirred. The
35 temperature conditions while the solution is maintained in the pH

range are not particularly limited; however, the temperature is preferably room temperature.

[0067]

5 In the deacetylation step, at least a base is added to a solution to be subjected to the deacetylation step (e.g., a solution containing acidic xylooligosaccharide). As long as the desired pH can be achieved, the base to be added is not particularly limited, and is preferably sodium hydroxide.

[0068]

10 The deacetylation step may comprise a pH adjustment step of adjusting, to less than pH 11, a solution having pH 11 or more due to a base added after the solution is maintained at the pH described above. In the pH adjustment step, the solution may be adjusted to, for example, pH 9 or less, pH 8 or less, pH 7 or
15 less, pH 6 or less, pH 5 or less, pH 4 or less, or the like. The adjustment may be performed by adding an acid. Examples of acids include hydrochloric acid.

[0069]

20 The deacetylation step may also preferably comprise a desalting step after the pH adjustment step. Desalting can be performed, for example, using a dialysis membrane or an NF membrane.

[0070]

25 The deacetylation step may further comprise a step of powdering the obtained product for the subsequent treatment.

[0071]

Other Steps

Molecular Weight Adjustment Step

30 The method for producing pentosane polysulfate may further comprise a molecular weight adjustment step between the first step and the second step. The molecular weight adjustment step may be performed either before or after the deacetylation step. Fig. 2 is a flow diagram including a molecular weight adjustment step between the first step and the second step. As
35 shown in Fig. 2, in the molecular weight adjustment step, the

molecular weight of the acidic xylooligosaccharide obtained in the first step is adjusted. For example, in the molecular weight adjustment step, the molecular weight of the acidic xylooligosaccharide can be reduced.

5 [0072]

In the molecular weight adjustment step, a pentosan polysulfate having a weight average molecular weight of 1000 or more and 30000 or less can be obtained by performing a treatment such as acid treatment, alkali treatment, enzyme treatment, NF
10 membrane treatment, UF membrane treatment, RO membrane treatment, gel filtration treatment, activated carbon treatment, ion exchange treatment, or electrodialysis treatment. In the molecular weight adjustment step, a membrane treatment or the like may be performed to selectively recover pentosan polysulfate
15 having a desired weight average molecular weight.

[0073]

Post-Molecular-Weight-Adjustment Separation and Purification Step

The method for producing pentosan polysulfate may further comprise a post-molecular-weight-adjustment separation
20 and purification step performed after the molecular weight adjustment step. Examples of the post-molecular-weight-adjustment separation and purification step include gel filtration, ion exchange, NF membrane treatment, UF membrane treatment, RO
membrane treatment, electrodialysis treatment, activated carbon
25 treatment, water-soluble organic solvent treatment, chromatographic treatment, and the like. When the production method includes such a post-molecular-weight-adjustment separation and purification step, acidic xylooligosaccharide with
a desired molecular weight obtained in the molecular weight
30 adjustment step can be selectively recovered, and pentosan polysulfate having a narrow molecular weight distribution can be efficiently obtained.

[0074]

The weight average molecular weight (M_w) of pentosan
35 polysulfate obtained by the production method of the present

invention is not particularly limited; and may be, for example, 5000 or less, 4000 or less, 3900 or less, 3800 or less, or 3750 or less. In this case, the lower limit of the weight average molecular weight (Mw) of the pentosan polysulfate is preferably
5 1000.

The weight average molecular weight (Mw) of pentosan polysulfate may be, for example, more than 5000, 6000 or more, 7000 or more, 10000 or more, 15000 or more, or 20000 or more.
[0075]

10 The number average molecular weight (Mn) of pentosan polysulfate is not particularly limited; and may be, for example, 5000 or less, 4000 or less, 3900 or less, 3800 or less, or 3750 or less. In this case, the lower limit of the number average molecular weight (Mn) of pentosan polysulfate is preferably 300.

15 The number average molecular weight (Mn) of pentosan polysulfate may be more than 5000, may be 6000 or more, may be 7000 or more, may be 10000 or more, may be 15000 or more, or may be 20000 or more.
[0076]

20 The weight average molecular weight (Mw) and the number average molecular weight (Mn) of pentosan polysulfate obtained by the production method of the present invention can be measured by GPC (gel permeation chromatography). As the GPC column, a YMC-Pack Diol-300 and YMC-Pack Diol-60 (both manufactured by YMC)
25 connected to each other can be used. The GPC conditions can be, for example, the following conditions.
Eluent: 25 mM potassium dihydrogen phosphate/25 mM dipotassium hydrogen phosphate/50 mM potassium chloride
Flow rate: 0.7 mL/min
30 Measurement temperature: 40°C
Detector: refractive index detector
Analysis time: 40 minutes
[0077]

The degree of dispersion of pentosan polysulfate
35 obtained by the production method of the present invention is

preferably 1.00 or more and 1.40 or less, more preferably 1.00 or more and 1.35 or less. The degree of dispersion of pentosan polysulfate is further preferably 1.00 or more and 1.20 or less.

The degree of dispersion (D) of pentosan polysulfate is

5 calculated by the following formula:

Degree of Dispersion (D) = Weight average molecular weight (Mw)/Number average molecular weight (Mn)

[0078]

10 The pentosan polysulfate obtained by the production method of the present invention has high purity, and tends to have a narrow molecular weight distribution. The pentosan polysulfate obtained by the production method of the present invention has excellent quality stability.

[0079]

15 Applications of Pentosan Polysulfate

The pentosan polysulfate obtained by the production method of the present invention can be used for pharmaceuticals, foods, cosmetics, and like purposes. For example, a pharmaceutical composition containing, as an active ingredient, 20 the pentosan polysulfate obtained by the production method of the present invention (pentosan polysulfate, pharmaceutically acceptable salt of pentosan polysulfate, or pharmaceutically acceptable solvates thereof) can be provided. In particular, since pentosan polysulfate has anticoagulant activity, the above 25 pharmaceutical composition can be used as an anticoagulant.

[0080]

In general, anticoagulant activity is based on the activity of inhibiting blood coagulation factors. That is, when anticoagulant activity is high, a blood coagulation reaction is 30 inhibited. Blood coagulation factors refer to the action system of a series of molecules in a living body for coagulating blood when bleeding etc. Successive activation of a large number of blood coagulation factors agglutinates fibrin, and stops bleeding in the bleeding area. Representative examples of blood 35 coagulation factors include factor Xa and factor IIa. Blood

coagulation can be inhibited by inhibiting the activity of these factors.

[0081]

5 The factor Xa inhibitory activity (anti-Xa activity) of pentosan polysulfate is preferably 0.10 IU/mg or more, and more preferably 0.12 IU/mg or more.

The factor IIa inhibitory activity (anti-IIa activity) of pentosan polysulfate is preferably 0.50 IU/mg or less, more preferably 0.40 IU/mg or less, and even more preferably 0.30
10 IU/mg or less.

[0082]

Here, the factor Xa inhibitory activity (anti-Xa activity) can be measured using Test Team (registered trademark) Heparin S (manufactured by Sekisui Medical Co., Ltd.).

15 The factor IIa inhibitory activity (anti-IIa activity) can be measured using Biophen heparin anti-IIa (manufactured by Hyphen BioMed).

[0083]

The activity ratio of the factor Xa inhibitory activity
20 (anti-Xa activity) of pentosan polysulfate to the factor IIa inhibitory activity (anti-IIa activity) of pentosan polysulfate is preferably within a predetermined range. More specifically, the anti-Xa activity/anti-IIa activity ratio is preferably 0.50 or more, more preferably 1.00 or more, even more preferably 1.10
25 or more, and still even more preferably 1.20 or more.

The production method of the present invention can provide a pentosan polysulfate that has anti-Xa activity, anti-IIa activity, and anti-Xa activity/anti-IIa activity ratio controlled within the ranges described above. That is, a pentosan
30 polysulfate that has anti-IIa activity lower than anti-Xa activity can be provided. When the anti-Xa activity/anti-IIa activity ratio is controlled to fall within the above-mentioned range, the anticoagulant activity can be more effectively increased; and the occurrence of side effects, such as an
35 increased risk of bleeding or a decrease of platelets, can be

suppressed.

[0084]

Pharmaceutical compositions comprising pentosan polysulfate obtained by the production method of the present invention can be used, for example, as surface treatment agents for medical devices or medical materials. Such a pharmaceutical composition can be used, for example, as a surface treatment agent for implantable artificial organs, artificial blood vessels, catheters, stents, blood bags, contact lenses, intraocular lenses, and surgical auxiliary instruments. As a method for immobilizing the pharmaceutical composition on the surface of a medical device or a medical material, there is, for example, a method comprising allowing the pharmaceutical composition to be in contact with a medical device or a medical material, and irradiating the contact portion with a radiation beam.

Such pharmaceutical compositions can be used as oral agents or external preparations.

20 Examples

[0085]

The features of the present invention are described below more specifically with reference to Production Examples. The materials, amounts used, proportions, treatment content, treatment procedures, and the like described in the following Production Examples can be appropriately changed as long as such changes do not depart from the spirit of the present invention. Accordingly, the scope of the present invention should not be construed as being limited by the following specific examples.

30 [0086]

Example 1

Production of Acidic Xylooligosaccharide

Forty parts by mass of water was added to 10 parts by mass of wood chips (hardwood), and a heat treatment was performed at 160°C for 3 hours. The resulting mixture was then subjected to

solid-liquid separation using a Screw Press (manufactured by Shinryo Seisakusho: 250 × 1000 SPH-EN), and the filtrate was recovered. The filtrate was further filtered through a bag filter with a micron rate of 1 μm (manufactured by ISP Filters). After 5 parts by mass of activated carbon (PM-SX; manufactured by Mikura Kasei Kabushiki Kaisha) was added to treat the filtrate at 50°C for 2 hours, the treatment mixture, including the activated carbon, was further filtered through a ceramic filter with a micron rate of 0.2 μm (manufactured by Nihon Pall Co., Ltd.) to recover a clear filtrate. After the clear filtrate was concentrated 20 times with a reverse osmosis membrane (NTR-7450; manufactured by Nitto Denko Corporation) to obtain a concentrated sugar liquid, the concentrated sugar liquid was passed at SV 1.5 through a 4-bed 4-tower type ion exchange resin system consisting of a strong cationic resin (PK-218; manufactured by Mitsubishi Chemical Corporation), a weak anionic resin (WA30; manufactured by Mitsubishi Chemical Corporation), a strong cationic resin (PK-218; manufactured by Mitsubishi Chemical Corporation), and a weak anionic resin (WA30; manufactured by Mitsubishi Chemical Corporation). Acidic xylooligosaccharide was adsorbed on the weak anionic resin of the second and fourth towers. A 50 mM sodium chloride aqueous solution was then passed through the second and fourth towers at SV 1.5 to recover an acidic xylooligosaccharide solution with an average polymerization degree of less than 8. Sodium hydroxide was added to the obtained acidic xylooligosaccharide solution to achieve the pH shown in the table, and the resulting mixture was stirred for the period of time shown in the table for deacetylation. Hydrochloric acid was added to the obtained solution to achieve a pH of less than 5, and desalting was performed using a dialysis membrane (Spectra/Por; manufactured by Spectrum). The obtained acidic xylooligosaccharide solution was powdered using a freeze-drying machine (manufactured by Eyela).

[0087]

35 Production of Pentosan Polysulfate Sodium

10 mL of N,N-dimethylformamide, 2.4 g of sulfur trioxide pyridine complex, and 0.3 g of the acidic xylooligosaccharide powder produced by the above-described method were added to a 100 mL separable flask, and allowed to react at
5 40°C for 3 hours. After cooling, the obtained reaction mixture was added dropwise to 500 mL of ethanol. The generated precipitate was collected by filtration, and 30 mL of water was added to dissolve the precipitate therein. A sodium hydroxide solution was added to this solution to achieve a pH of 10. The
10 resulting solution was added dropwise to 500 mL of ethanol, and the obtained precipitate was collected by filtration. Thereafter, 50 mL of water was added to dissolve the precipitate therein. After activated carbon was added to the solution and stirred, the resulting mixture was filtered. The filtrate was concentrated
15 using an evaporator, and powdered using a freeze-drying machine (manufactured by Eyela).

[0088]

Acetyl group content

35 mg of sodium 3-(trimethylsilyl)propionate-2,2,3,3-d₄
20 (Isotec Corporation) was dissolved in heavy water (Kanto Kagaku). Using a 25-mL measuring flask, the solution was diluted to prepare an internal standard solution. The pentosan polysulfate sodium obtained in each of the Examples and Comparative Examples was weighed (30 mg), and dissolved in 1 mL of the internal
25 standard solution to prepare a solution for NMR analysis. The obtained solution was transferred to an NMR sample tube (Kanto Kagaku), and ¹H-NMR measurement was performed using FT-NMR (JNM-LA400; JEOL Ltd.). The acetyl group content was calculated from the integral ratio of the acetyl peak of pentosan polysulfate
30 sodium to the trimethylsilyl peak of the internal standard substance.

[0089]

Weight Average Molecular Weight of Pentosan Polysulfate Sodium

The weight average molecular weight (M_w) of pentosan
35 polysulfate sodium shown in Table 1 was measured by GPC (gel

permeation chromatography). As the GPC column, a YMC-Pack Diol-300 and YMC-Pack Diol-60 (both manufactured by YMC) connected to each other were used. GPC was performed under the following conditions.

5 Eluent: 25 mM potassium dihydrogen phosphate/25 mM dipotassium hydrogen phosphate/50 mM potassium chloride

Flow rate: 0.7 mL/min

Measurement temperature: 40°C

Detector: refractive index detector

10 Analysis time: 40 minutes

[0090]

Sulfur Content

The sulfur content of pentosan polysulfate sodium was measured by the oxygen flask combustion method described in the
15 Japanese Pharmacopoeia.

Measurement of Anti-Xa Activity

The anti-Xa activity of pentosan polysulfate sodium was measured using Test Team (registered trademark) Heparin S
20 (manufactured by Sekisui Medical Co., Ltd.).

Measurement of Anti-IIa Activity

The anti-IIa activity of pentosan polysulfate sodium was measured using Biophen heparin anti-IIa (manufactured by
25 Hyphen BioMed).

[0091]

Table 1

	Comparative Example 1	Example 1	Example 2	Example 3	Example 4	Example 5
Deacetylation conditions	No treatment	pH 11 1 hr	pH 11 2 hr	pH 12 0.5 hr	pH 12 1 hr	pH 13 3 hr
Weight average molecular weight	2211	2356	2325	2178	2129	2155
Acetyl group content (Mass%)	2.793	1.618	0.866	0.470	0.217	0.000
Sulfur content	16.27	14.33	15.12	15.09	15.34	15.28

(mass%)						
Anti-IIa activity (IU/mg)	0.0221	0.1405	0.1845	0.0676	0.0934	0.0976
Anti-Xa activity (IU/mg)	0.0840	0.2047	0.2588	0.2439	0.2419	0.2297
Anti-Xa/anti-IIa activity ratio	3.801	1.457	1.403	3.607	2.591	2.352

[0092]

The anti-IIa activity and anti-Xa activity in Table 1 are also shown in a graph (Fig. 3).

As can be seen from the results shown in Table 1 and Fig. 3, pentosan polysulfate sodium with a low acetyl group content obtained by any one of the production methods described in the Examples exhibits a preferable anti-Xa/anti-IIa activity ratio, and has anti-Xa activity higher than that of pentosan polysulfate sodium obtained by the production method described in the Comparative Example.

[0093]

Table 2 shows the yield of pentosan polysulfate sodium when pentosan polysulfate sodium was obtained from acidic xylooligosaccharide powder under the conditions described in Comparative Example 1 or Example 5.

[0094]

Table 2

Comparative Example 1	Example 5
About 18.1% (yield: 0.1391 g, amount added: 0.3072 g)	About 40.9% (yield: 0.3181 g, amount added: 0.3108 g)

[0095]

As can be seen from the results in Tables 1 and 2, when using the production method of the present invention, pentosan polysulfate sodium that exhibits a preferable anti-Xa/anti-IIa activity ratio, and that has sufficiently high anti-Xa activity, can be produced with a high yield.

CLAIMS

[Claim 1]

A method for producing pentosan polysulfate, comprising
a first step of obtaining an acidic xylooligosaccharide
5 from a plant-derived raw material; and
a second step of obtaining pentosan polysulfate from
the acidic xylooligosaccharide,
the first step comprising a step of depolymerizing the
plant-derived raw material,
10 the second step comprising a step of sulfating the
acidic xylooligosaccharide; and
the method comprising a deacetylation step of adding a
base to achieve a pH of 11 or higher, the deacetylation step
being a step performed after the depolymerization step.

15 [Claim 2]

The method for producing pentosan polysulfate according
to claim 1, wherein the deacetylation step comprises stirring a
solution containing the acidic xylooligosaccharide at a pH of 11
or higher for 1 hour or more.

20 [Claim 3]

The method for producing pentosan polysulfate according
to claim 1, wherein the deacetylation step comprises stirring a
solution containing the acidic xylooligosaccharide at a pH of 12
or higher for 0.5 hours or more.

25 [Claim 4]

The method for producing pentosan polysulfate according
to any one of claims 1 to 3, wherein the base is sodium
hydroxide.

[Claim 5]

30 The method for producing pentosan polysulfate according
to any one of claims 1 to 4, wherein the depolymerization step is
performed under non-alkaline conditions.

[Claim 6]

The method for producing pentosan polysulfate according
35 to any one of claims 1 to 5, wherein the depolymerization step is

a heat treatment step.

[Claim 7]

The method for producing pentosan polysulfate according to claim 6, wherein the heat treatment step is a step of heating
5 to 120°C or higher under non-alkaline conditions.

[Claim 8]

The method for producing pentosan polysulfate according to any one of claims 1 to 7, wherein the plant-derived raw material is a wood-derived raw material.

10 [Claim 9]

The method for producing pentosan polysulfate according to any one of claims 1 to 8, further comprising a molecular weight adjustment step between the first step and the second step.

15 [Claim 10]

The method for producing pentosan polysulfate according to claim 9, further comprising a post-molecular-weight-adjustment separation and purification step performed after the molecular weight adjustment step.

20 [Claim 11]

The method for producing pentosan polysulfate according to any one of claims 1 to 10, wherein the second step further comprises a post-sulfation purification step performed after the sulfation step.

25 [Claim 12]

The method for producing pentosan polysulfate according to claim 11, wherein the second step further comprises a powdering step performed after the post-sulfation purification step.

30 [Claim 13]

A pentosan polysulfate produced by the production method according to any one of claims 1 to 12.

[Claim 14]

The pentosan polysulfate according to claim 13, which
35 has an acetyl group content of 0 to 2.0 mass%.

[Claim 15]

An anticoagulant comprising the pentosan polysulfate according to claim 13 or 14.