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(54) Title: COMPOSITION CONTAINING GINSENG EXTRACT COMPRISING SAPONIN DERIVATIVES ISOLATED FROM GINSENG RADIX AND GINSENG FOR PREVENTING AND TREATING SCRATCHING DISEASES

(57) Abstract: The present invention relates to a composition for the prevention and treatment of scratching disease containing at least one ginseng extract selected from the group consisting of ginseng or ginseng steamed red, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom as effective components.
COMPOSITION CONTAINING GINSENG EXTRACT
COMPRISING SAPONIN DERIVATIVES ISOLATED FROM
GINSENG RADIX AND GINSENG FOR PREVENTING AND
TREATING SCRATCHING DISEASES

TECHNICAL FIELD

The present invention relates to a composition for preventing or treating scratching diseases (pruritus) containing at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom as effective components.

Backgrounds

Scratching diseases (pruritus), which is also called itch, can be defined as a sensation that provokes a desire to scratch. Itch can be produced by diverse stimuli such as touch, a sudden temperature change, mental stress, and physical, chemical, electrical or thermal stimuli. Especially, anxiety or fear can also produce severe itch. Generally one gets itchy the most before going to bed. Areas of a body that are especially prone to itch are the external auditory meatus, eyelids, nostrils, and vulva.
The development mechanism of scratching diseases (pruritus) involves chemical materials such as histamine, kinin, protease, prostaglandin and etc. The severity of itch varies depending on persons. Even a person can show different reactions to the same stimulus.

Scratching diseases (pruritus) include paroxysmal scratching diseases such as lichen simplex chronicus, atopic dermatitis, dermatitis herpetiformis, which are very serious, chronic and recurring scratching diseases; men’s scrotum scratching diseases and vulvar scratching diseases due to the mental-related facts as induced by candidiasis, trichomonas vaginitis, contact dermatitis caused by contact with pad, contraceptive, vagina cleansing lotion and condom, urinary incontinence, diabetes mellitus, sclerosing atrophic chronicus; and scratching diseases that are related to itchy skin diseases induced by dermatitis herpetiformis, insect bites, scab, atopic dermatitis, contact dermatitis, psoriasis, nummular eczema, chronic simplex chronicus, erythema prurigo, systemic dermatitis.

To treat these scratching diseases, proper topical embrocation such as steroid is often selected and used for
localized itch, and antihistamines are administered to relieve an itch over the body. However, these chemical synthetic medicaments can cause serious side effects, and thus developing a substance that can substitute them is urgent in the pertinent art.

Detailed description of the invention

Technical Problem to be solved

Accordingly, the present inventors have been conducting numerous researches in order to develop natural substances that can substitute the chemical synthetic medicaments for treating scratching diseases which have serious side effects. As a result, the present inventors have found that at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom has excellent effects for preventing and treating scratching diseases and that as natural substances, they do not produce side effects to the human body at all.

Accordingly, the object of the present invention is to provide a new composition for preventing or treating scratching diseases.
Technical Solutions

In order to achieve the object described above, the present invention provides a composition for preventing or treating scratching diseases containing at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom as effective components.

In addition, the present invention provides a method of preventing or treating scratching diseases comprising administration of at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom to patients in need.

In addition, the present invention provides a use of at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom for manufacturing of medicament for preventing or treating
scratching diseases.

Specifically, the present invention provides, as a ginseng saponin derivative isolated from said ginseng extract, at least one ginseng saponin derivatives selected from the group consisting of panaxytriol, panaxydol, panaxynol, ginsenoside Rc, ginsenoside Rb1, Rb2, ginsenoside Rg3, compound K, ginsenoside Rh2, 20(R)-ginsenoside Rh2, 20(R)-protopanaxadiol, 20(S)-protopanaxadiol, ginsenoside Rh1, and 20(S)-protopanaxatriol, desirably, a composition having in particular compound K(20-O-β-glucopyranosyl-20(S)-Protopanaxadiol), ginsenoside Rg3 and ginsenoside Rh2 as effective components, for preventing or treating scratching diseases.

A composition of the present invention for preventing or treating scratching diseases comprises 0.02-90% by weight of said ginseng extract and ginseng saponin derivatives isolated therefrom with respect to the total weight of the composition.

As for the terms used in the present specification, ginseng extract includes extracts from ginseng or red
ginseng extract and can be used as a generic term for products obtained by fermenting said extracts from ginseng or red ginseng by lactic-acid or intestinal bacteria. A composition for preventing or treating scratching diseases according to the present invention is characterized in that it comprises a ginseng extract in its generic meaning.

Also, ginseng saponin derivatives mean pharmacological components included in the ginseng extract. It not only comprises saponin already known in the pertinent art, but also unknown ginseng saponin derivatives included in ginseng extracts that could provide pharmacological components.

Hereinafter, the present invention is described in more detail.

Ginseng is perennial plants belonging to Panax species of the Araliaceae, and approximately 11 species of ginseng are known so far. Typical species are; (1) Korea Insam (Panax ginseng C.A. Meyer) grows in the Far Eastern Asia region (at a latitude of 33-48°N: Korea, North Manchuria, part of Russia) and its pharmacological effects are excellent; (2) U.S. ginseng (Panax quinquefolium L.) grows
and is cultivated in the U.S. and Canada; (3) Panax notoginseng F.H.Chen grows and is cultivated from the southeastern Yunnan to the southwestern Guangxi Zhuangzu in China; and (4) Panax japonicus C.A. Meyer grows in Japan, Southernwestern parts of China, and Nepal (Hwa Han Yak Baek Kwa Do Ram, Volume 1 at page 1-8, Nambatsunehiki, Hoiku Corp., 1980).

Meanwhile, according to the treatment of ginseng, it can be classified into fresh ginseng (not dried after being picked up from the field); white ginseng (a fresh ginseng dried at a room temperature); and red ginseng (a fresh or white ginseng heated at 98-100).

The pharmacological effects of these ginsengs are excellent and recorded in Shin Nong Bon Cho Kyung, a medical book. Through many medical experiments, ginseng is proven to have the effects of strengthening a non-specific resistance of the body against stress, acid-oxidant function, treatment for hypertension, reinforcing the function of insulin, lowering a blood glucose level in rats with diabetes induced by alloxan RNA synthesis of white rat's liver, protein synthesis, stimulating sugar and lipid metabolism, and preventing cancer. In addition, as a herb
medicine, it has been used to treat various kinds of diseases such as psychiatric diseases, nervous system diseases and diabetes. Saponin, the major component of ginseng, has proven to have effects such as developing stamina and health, calming down, hematosis and antihypertensive effects (Nambatsunehiki et al., Hwa Han Yak Baek Kwa Do Ram, 1, pp 1-8, 1980).

The pharmacological effects of ginsenoside components as saponin or its derivatives included in ginseng has been revealed. Table 1 below shows the results.

Table 1

<table>
<thead>
<tr>
<th>The types of ginsenoside</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsenoside-Rb1</td>
<td>The central nerve system suppression function and mental stability; feeding center suppression; suppression of aggressive behavior; alleviating pain; anti-convulsion; antianxiety; adrenocorticotropic hormone and corticosteroid secretion promotion; cholesterol biosynthesis promotion; memory improvement; decrease in high cholesterol, neutral fat and free fatty acid; nerve cell survival promotion; liver protection; myeloid cell's DNA, RNA, protein and lipid synthesis promotion; acetylcholine emission promotion; vasodilution; platelet agglutination inhibition; lipid peroxidation inhibition; cholesterol metabolism promotion; anti-inflammation; phagocytic function activation; kidney glomerular hypertrophy suppression</td>
</tr>
<tr>
<td><strong>Ginsenoside-Rb2</strong></td>
<td>Sugar and fat metabolism promotion; anti-diabetic function; nitrogen metabolism balancing maintenance; protein and lipid synthesis promotion; high cholesterol decrease and anti-arteriosclerosis; cancer toxin hormone's antagonism; smooth muscle cell breeding inhibition; DNA, RNA, adrenocorticotropic hormone and corticosteroid secretion promotion; stimulating appetite lost by stress; tumor blood vessel neogenesis inhibition; antioxidation active material formation promotion; ATP supply activation in liver tissue; immunoregulation; cholesterol metabolism promotion; liver cell growth and DNA synthesis promotion; blood platelet agglutination inhibition; alleviating pain</td>
</tr>
<tr>
<td><strong>Ginsenoside-Rc</strong></td>
<td>Liver, blood serum cholesterol and RNA synthesis promotion; myeloid cell DNA and RNA, protein and lipid synthesis promotion; alleviating pain; corticosteroid secretion promotion; prostacyclin biosynthesis promotion; kidney glomerular hypertrophy suppression</td>
</tr>
<tr>
<td><strong>Ginsenoside-Rd</strong></td>
<td>adrenocorticotropic hormone and corticosteroid secretion promotion; kidney glomerular hypertrophy suppression</td>
</tr>
<tr>
<td>Compound</td>
<td>Function</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ginsenoside-Re</td>
<td>adrenocorticotropic hormone and corticosteroid secretion promotion; alleviating pain; vasodilation; anti-heat stress; smooth muscle cell breeding supression; myeloid cell's DNA, RNA, protein and lipid synthesis promotion; liver protection; cholesterol metabolism promotion</td>
</tr>
<tr>
<td>Ginsenoside-Rgl1</td>
<td>immune function enhancement; blood platelet agglutination inhibition; anti-thrombin; good use activation; memory and learning function improvement; ant-fatigue; anti-stress; stimulating central nerve system; vasodilation; anti-inflammation; anti-nephritis and renal blood flow enhancement function; protection functions against harmful stimuli such as heat and endogenous pyrogen; improving movement impediment caused by stress; nerve cell survival rate promotion; liver cell breeding and DNA synthesis promotion; adrenocorticotropic hormone secretion promotion; cholesterol metabolism promotion; liver protection function</td>
</tr>
<tr>
<td>Ginsenoside-Rhl</td>
<td>Experimental liver injury inhibition function; tumor cell differentiation promotion; inhibition of blood platelet agglutination; good use activation function, anti-inflammation effect; anti-allergy effect</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ginsenoside-Rh2</td>
<td>Inhibition of Cancer cell breeding; promotion of inducement of cancer cell redifferentiation; inhibition of cancer cell invasion; inhibition of tumor breeding; supporting anti-cancer medicine with its anti-cancer activity; anti-allergy effect; anti-inflammation effect</td>
</tr>
<tr>
<td>Compound K</td>
<td>Strong tumor blood vessel neogenesis function and cancer cell metastasis inhibition function; block of IV type collagenase secretion; anti-neogenesis blood vessel formation activity and blood platelet agglutination inhibition; anti-allergy effect; anti-inflammation effect</td>
</tr>
</tbody>
</table>

The effective components of ginsenoside that produce the main pharmacological effects of ginseng are saponins such as ginsenoside-Rb1, Rb2 and Rc. However, the components that have the effects such as anti-cancer function, inhibition of cancer metastasis, or anti-allergy function are saponins such as compound K (20-O-β-glucopyranosyl-20(S)-Protopanaxadiol), ginsenoside-Rh1 and Rh2, and A 20-ginsenoside-Rh2, which are included in ginseng in a very little amount. The components that produce the effects of ginseng, such as anti-cancer and anti-allergy functions and enhancing immune function, have been known to be saponin components such as compound K (20-
0-β-glucopyranosyl-20(S)-Protopanaxadiol, ginsenoside-Rh1 and Rh2, and Δ20-ginsenoside-Rh2, which are included in a ginseng in a very little amount.

However, documents that have been published so far do not describe or suggest that a composition containing ginseng is effective in treating or preventing scratching diseases.

According to the present invention, it is found that the following components are effective in treating and preventing scratching diseases (itch; pruritus): at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom such as compound K, ginsenoside Rf, ginsenoside Rg3 and ginsenoside Rh2.

The present inventors have found that even though ginseng extracts from red ginseng produced according to the prior art contain a significant amount of ginsenoside Rg3, other saponin components such as compound K and ginsenoside Rh2 are not increased significantly. Also, the present inventors have found that if ginseng or red ginseng
extracts are fermented by lactic-acid bacteria, compound K is increased significantly; however, in the case of ginseng lactic-acid bacteria ferment extracts, ginsenoside Rh2 is not increased significantly, but ginsenoside Rh2 is shown to be increased significantly only in red ginseng lactic-acid or intestinal bacterial ferment extracts.

Hereinafter, a process for preparing ginseng extract to be contained in a composition for preventing or treating scratching diseases (pruritus) is explained according to the present invention. However, it should be understood that the present invention is not limited to the following processes in any manner, and that processes for preparing red ginseng and for preparing lactic-acid bacteria ferment known in the art can be applied to the present invention.

(1) Washing and Drying process

In order to remove foreign bodies, a fresh ginseng was washed in water or in water containing 0.1% of acetic acid and then dried. Using water containing acetic acid is effective in removing contaminated bacteria and thus is preferable.
(2) Process for Preparing Red Ginseng

Red ginseng was obtained by steaming the washed ginseng obtained in process (1) at 98-100°C for 1 to 10 hours, preferably for 2 to 5 hours with a commercially available red ginseng maker and then drying it at 60°C for 5 hours with a common drying machine. Other necessary conditions and supplementary matters with regard to the process for preparing red ginseng are widely known in the pertinent art, and red ginseng which can be used for the process for preparing red ginseng according to the present invention can be prepared by the known method.

(3) Extracting Process

Saponin components were extracted from ginseng or red ginseng by extracting for 3 hours from and concentrating dried white ginsens including fresh ginsens and red ginsens, using water or alcohol or a mixture of water and alcohol (preferably 70% of alcohol), are to fifty times as much (weight/volume), for 1 hour to two days, preferably for three hours at a temperature of 20 to 80°C, preferably from 50 to 60 °C.
Ginsengs applicable to this process include ginsengs, processed ginseng products and by-products, preferably fresh ginsengs, red ginsengs, white ginsengs, fine roots of ginseng, ginseng leaves, ginseng extracts and powdered ginseng. Ginseng extracts of these kinds can be optionally used in the below-mentioned bioconversion process.

(4) Bioconversion Process

Biologically fermented ginseng ferments were obtained by adding lactic-acid bacteria or intestinal bacteria to water extracts of fresh ginsengs, white ginsengs and red ginsengs, or concentrated water suspension of 70% alcohol extracts, and then culturing them at a temperature of 20 to 50°C, preferably 25 to 40°C for six hours to five days, preferably 24 hours to 48 hours. Here, fermenting time and fermenting temperature can be adequately chosen depending on the strain used and for extracting efficiency.

(5) Concentrating or Lyophilizing Process

The ginseng ferment extracts obtained in the above process (4), specifically white ginseng or red ginseng extracts can be used either as they are or are lyophilized
for the present process. Or, they can be used after they are extracted with water or alcohol and the supernatant is concentrated or dried. This concentrating or lyophilization method has been widely known in the pertinent art.

In the above series of processes, the process of preparing red ginsengs converts ginsenoside-Rb1, ginsenoside-Rb2, ginsenoside-RC, etc., included in ginsengs to ginsenoside-Rg3, and the bioconversion process through lactic-acid bacteria or intestinal bacteria can convert thus obtained ginsenoside-Rg3 to the final metabolic product ginsenocide Rh2. Direct bioconversion of white ginseng and fresh ginseng can convert ginsenoside-Rb1, ginsenoside-Rb2, ginsenoside-Rc to compound K only.

For the above-mentioned bioconversion, if it can metabolize ginseng saponins and produce bioconverted compound ginsenoside Rh2, it is satisfactory to use any lactic acid bacteria, preferably a Bifidobacterium genus, more preferably one selected from Bifidobacterium infantis, B.bifidum, Lactobacillus lactis, Clostridium butyricum, Bifidobacterium H-1 (KCCM 10493), Bifidobacterium KK-1 (KCCM 10364), Bifidobacterium KK-2(KCCM 10365), one of the
selected from Bifidobacterium KK-11 (Kyung Hee University, College of Medicine, Professor Kim Dong-hyun) or their mixed strains.

For the above-mentioned bioconversion, if it can metabolize ginseng saponins and produce bioconverted compounds compound K or ginsenoside Rh2, any intestinal bacteria can be used, preferably intestinal bacteria of genus Bacterioides, genus Fusobacterium, genus Eubacterium, more preferably Bacterioides JY-6 (Kyung Hee University, College of Medicine, Professor Kim Dong-Hyun, Biol. Pharm. Bull., 23, pp1481-1485,2000), Fusobacterium K-60 (Kyung Hee University, College of Medicine, Professor Kim Dong-hyun, Biol. Pharm. Bull., 23, pp1481-1485,2000), Eubacterium L-8 (Kyung Hee University, College of Medicine, Professor Kim Dong-hyun, Biol. Pharm. Bull., 23, pp1481-1485,2000)

Meanwhile, according to the present invention, the above process (5) is optional while processes (3) and (4) are successive, essential processes if processes (1) and (2) are carried out; in process (4) red ginseng extract and strain can be mixed and prepared in a capsule so that they can be reacted in the human intestines without the process of cultivating them; and processes (3) and (4) can be
carried out right after process (1) without going through process (2) where a red ginseng is prepared, and all of these processes can be optionally adopted according to the type of a final product.

In addition, the following processes can be carried out additionally.

Process of lyophilization wherein ginseng extract of process (5) is concentrated or lyophilized without additional treatment of it;

Process wherein impurities and precipitation are removed from the bioconverted ginseng extract obtained in process (3) by subjecting the ginseng extract obtained in process (5) to centrifugal separation, filtering the supernatant and concentrating the remaining liquid in vacuo, and simultaneously the extract is concentrated and then goes through a process of drying such as lyophilization;

As an extract process wherein only effective components contained in the ginseng extract obtained in process (5) is extracted by using a proper solvent, a process that uses as a proper solvent, water, methanol, and a low-quality
alcohol solution such as ethanol and a particular method such as supercritical (fluid) extraction to extract effective components included in ginseng extract obtained in process (5), and a drying process by lyophilization that follows the previous process.

Agitation or dilution process to produce processed drinks or food

The ratio of (ginsenoside Rh2+compound K)/(ginsenoside Rg3+Rc+Rd+Rb1+Rb2) of the ginseng extract of the present invention obtained after going through processes (1) to (4) including the red ginseng producing process, can be over 0.1.

The ratio of (compound K+ginsenoside Rd)/(ginsenoside Rc+Rd+Rb1+Rb2) of the ginseng extract of the present invention obtained after going through processes (1), (3) and (4), skipping the red ginseng preparation process (process (2)), can be over 0.1.

Additionally, the present invention can isolate ginsenoside Rh2 by extracting the ginseng ferment extract obtained after going through processes (1) to (4) by BuOH,
concentrating it, and then carrying out the silica gel column chromatography (5x50 cm, elution solvent: chloroform:methanol=20:1); and from the extract obtained going through processes (1), (3) and (4), skipping the red ginseng preparation process, compound K can be isolated under the same conditions are above.

Hereinafter, a detailed explanation on the applications of the composition for preventing and treating scratching diseases according to the present invention follows.

The composition according to the present invention for preventing or treating scratching diseases containing at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom as effective components, can be produced in various commercial types of ginseng products by adding an optional substance or carrying out another optional process, as long as it does not negatively affect the effects of preventing and treating scratching diseases.

Types of ginseng products include, but are not limited
to, for example, ginseng dried powder, extracts, ampoules, teas and tablets.

Additionally, compositions containing extracts or compounds of the present invention can be prepared as a pharmaceutical preparation further including an adequate carrier, an excipient or a diluent according to commonly known methods.

Carriers, excipients or diluents that can be added to the extracts of the present invention or compositions comprising saponin derivatives included therein as effective components are lactose, dextrose, sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia rubber, alginate, gelatin, calcium phosphate, calcium ciliate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, water, methyl hydroxybenzoate, talc, magnesium stearate and minerals.

Additionally, the extracts of the present invention or compositions comprising saponin derivatives included therein as effective components can be provided in oral dosage forms such as powders, granules, tablets, capsules,
suspensions, emulsions, syrups, aerosols, or be used as external applications, as suppositories, and as sterile water for injection or as cosmetics such as a soap, according to its ordinary method in the pertinent field.

The dosage of extracts of the present invention or saponin derivatives contained therein can differ according to the patient's age, sex and weight, but 0.1 to 100 mg/kg can be administered once or several times a day. Also, dosages of extracts and their compositions can be adjusted according to the route of administration, seriousness of the diseases, sex, weight and age. Accordingly, the above dosages do not, in any way, restrict the scope of the present invention.

The extracts of the present invention or compositions comprising saponin derivates included therein can be used in various types as discussed above in pharmaceuticals, foods, beverages and cosmetics for preventing and treating scratching diseases (pruritus). Foods to which extracts of the present invention or compositions including saponin derivates therein can be added are, for example, various foods, beverages, gums, teas, vitamin complexes, health supplement foods, and soap.
The extracts and compounds of the present invention by themselves are pharmaceuticals that can be used for preventing purposes for a long time without concerns about negative effects, because they do not have any toxins or side effects.

The extracts of the present invention or saponin derivatives included therein can be also added to food, beverages or cosmetics for preventing or treating scratching diseases. The amount of extracts of the present invention or saponin derivatives included therein can be 0.01 to 15 by weight % with respect to the total weight of the health supplement food or cosmetics, 0.02-20g/100 ml for beverages, preferably 0.1-1g (dry weight).

Health supplement foods or beverage compositions according to the present invention can optionally further include various flavoring agents or natural carbohydrate in a directed ratio. Examples of said natural carbohydrates include standard sugars such as monosaccharide (for example, glucose, fructose, etc.); disaccharide (for example, maltose, sucrose, etc.); and polysaccharide (for example, dextrin, cyclodextrin); and sugar alcohol (for example, xylitol, sorbitol and erythritol). Additionally, natural flavoring agents (thaumatin, stevia extracts, such as
rebaudioside A, glycyrrhizin, etc.) and synthetic flavoring agents (saccharin, aspartame) can be advantageously used as a flavoring agent. The ratio of said carbohydrate is 0.1-20g per 100 ml (100 g) of the composition of the present invention, preferably 0.5-5 g (dried weight).

The composition according to the present invention can further include various nutrients, vitamins, minerals (electrolyte), synthetic and natural flavoring agents, coloring agents, improving agent in case of cheese and chocolate, pectic acid and its salt, alginic acid and its salt, organic acid, protective colloidal thickener, pH controlling agent, stabilizer, preservative, glycerin, alcohol, carbonating agent for carbonated beverages.

Besides, the compositions of the present inventions can further comprise fruit pulps for manufacturing natural fruit juices, fruit juice drinks and vegetable drinks, and these components can be used independently or in combination. The ratio of these additives are not restricted, but usually range from about 0 to 20 by weight% per 100 by weight% of the present composition.

Meanwhile, the efficacy of the composition of the present invention on scratching diseases can be confirmed
in an in vivo experiment method to demonstrate the effect of azelastines (commercially available medical supplies) in inhibiting scratching disease by using animal models, wherein scratching disease is induced by compound 48/80, histamine, substance P, etc. of which the test methods are already established.

The above said method is carried out by intravenously injecting compound 48/80, histamine, substance P into the back of a mouse, etc., and then measuring its behavior (scratching, licking, etc.) made in response to itch. A test sample can be intraperitoneally administered 1 hour before or orally administered 3 hours before, and its inhibitory effect against the behavior made in response to itch can be measured.

Hereinafter, the present invention is more specifically explained with the following examples; however, it should be understood that the present invention is not limited to these examples in any way.

Example 1. Preparation of non-processed ginseng extract (1)

20g of sliced 5-year-old fresh ginseng bought at Kumsan
Ginseng Market was extracted with water 5 times as much, at 60°C for 5 hours, concentrated in vacuo with an evaporator (Eyela, KN-IN Evaporator, Japan) and dried with a lyophilizer (Samwon Freezing Engineering Co., Model No. SFDSM24L, Korea) to obtain 1g of non-processed white ginseng dried powder.

**Example 2. Preparation of processed ginseng extracts (2)**

1kg of 5-year-old fresh ginseng bought at Kumsam Ginseng Market was cleansed in water (in some cases, a step of cleaning it in 0.1 % of acetic acid can be added), steamed at 98 to 100 °C for 4 hours and dried at 60°C for 5 hours. Thus obtained red dry ginseng was extracted with 70% of alcohol to obtain red ginseng extracts. Obtained red ginseng extracts was concentrated, suspended in water, extracted with BuOH and concentrated to obtain red ginseng extracts.

**Example 3. Preparation of ginseng extract ferments (3)**

1kg of 5-year-old fresh ginseng bought at Kumsan Ginseng Market was cleaned in water and extracted with 70 % of alcohol to obtain white ginseng extract. Thus obtained
white ginseng extracts was suspended in sterile distilled water until it became 0.5% (to get 0.5% of suspension) and then Bifidobacterium H-1 strain (10g by wet weight) was added thereto and left for 24 hours and cultivated at 37°C for 72 hours and extracted with BuOH and concentrated to obtain 4g of processed ginseng.

Example 4. Preparation of red ginseng extract ferments (4)

1kg of 5-year-old fresh ginseng bought at Kumsan Ginseng Market was cleansed in water and then in water containing 0.1 % of acetic acid, steamed at 98-100°C for 4 hours and then dried at 60°C for 5 hours. Thus obtained dried red ginseng was extracted with 70% of alcohol to obtain ginseng extract. This red ginseng extract was suspended in sterile distilled water to get 0.5% of suspension and Bifidobacterium H-1 strain (10g by wet weight) was added and left for 24 hours and cultivated at 37°C for 72 hours, extracted with BuOH and concentrated to obtain 4g of red ginseng lactic acid bacteria ferment.

Example 5. Preparation of red ginseng intestinal ferment extracts
1kg of 5-year-old fresh ginseng bought at Kumsan Ginseng Market was cleansed in water and then in water containing 0.1% of acetic acid, steamed at 98-100°C for 4 hours, and dried at 60°C for 5 hours. Thus obtained dried red ginseng was extracted with 70% of alcohol to obtain red ginseng extracts. This red ginseng extracts were suspended in sterile distilled water to get 0.5% of suspension to which was added an intestinal bacteria aggregate (10g by wet weight of a fungus body obtained by suspending fresh excrements of human in tryptic soy broth), cultivated for 24 hours at 37°C in total 72 hours, extracted with BuOH and concentrated to obtain 4g of intestinal bacteria ferments of red ginseng.

Example 6. Preparation of compound K from ginseng intestinal bacteria ferment

1kg of 5-year-old fresh ginseng bought at Kumsan Ginseng Market was cleansed in water and extracted with 70% of alcohol, to obtain ginseng extracts. This ginseng extract was suspended in sterile distilled water to get 0.5% of suspension, to which was added an intestinal bacteria aggregate (10g by wet weight of a fungus body obtained by suspending fresh excrements of human in tryptic
soy broth), cultivated for 24 hours at 37°C in total 72 hours, extracted with BuOH and then concentrated to obtain 15g of processed ginseng, and subjected to silica gel column chromatography (column size: 5x50 cm, elution solvent, chloroform:methanol=20:1) to isolate 0.6g of compound K.

Example 7. Preparation of ginsenoside Rg3 and Rh2 from red ginseng intestinal bacteria ferments

1kg of 5-year-old fresh ginseng bought at Kumsan Ginseng Market was cleansed in water and then in water containing 0.1% of acetic acid, and then steamed at 98~100°C for 4 hours, dried at 60°C for 5 hours. Thus obtained dried red ginseng was extracted with 70% of alcohol to obtain red ginseng extracts. This red ginseng was suspended in a sterile distilled water to get 0.5% of suspension, to which was added intestinal bacteria aggregate (10g by wet weight of a bacteria body obtained by suspending fresh excrements of human in tryptic soy broth), cultivated for 24 hours at 37°C in total 72 hours, extracted with BuOH and then concentrated to obtain 15g of processed ginseng, and subjected to silica gel column chromatography (Column size: 5x50 cm, elution solvent, chloroform:methanol=20:1), to isolate 0.3g of ginsenoside
Rg3 and 0.2g of ginsenoside Rh2.

Example 8. Content analysis experiment

2g of each of the unprocessed fresh ginseng of said Example 1 and powder of the fractions of the processed ginseng BuOH extract of Example 2, 3, 4 was suspended in 100 ml of water, extracted 3 times with 100 ml of ether, respectively and concentrated in vacuo. Then, thus obtained concentrations were extracted 3 times with 100 ml of butanol, respectively and concentrated in vacuo. Thus obtained concentrations were dissolved in 100 ml of methanol to obtain fractions of 100 mg of saponin. Thus obtained products was subject to TLC (development solvent: CHI13:MeOH:H2O=65:35:10; spray reagent: 5 % sulphuric acid methanol solution; Detector, Shimadzu TLC Scanner CS-9301PC) for content analysis. The results thus obtained are shown in Table 2 below.

[Table 2]
<table>
<thead>
<tr>
<th>Ginsenoside</th>
<th>Rb1</th>
<th>13.4</th>
<th>5.8</th>
<th>2.8</th>
<th>2.9</th>
</tr>
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<tbody>
<tr>
<td>Ginsenoside</td>
<td>Rb2</td>
<td>8.9</td>
<td>3.4</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Ginsenoside</td>
<td>Rc</td>
<td>9.2</td>
<td>1.7</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Ginsenoside</td>
<td>Rd</td>
<td>3.3</td>
<td>1.0</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Ginsenoside</td>
<td>Rg3</td>
<td>&lt;1</td>
<td>5.7</td>
<td>&lt;1</td>
<td>2.7</td>
</tr>
<tr>
<td>$\Delta^{20}$-</td>
<td>Ginsenoside</td>
<td>Rg3</td>
<td>&lt;1</td>
<td>1.1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Compound K</td>
<td></td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>5.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Ginsenoside</td>
<td>Rh2</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1.8</td>
</tr>
<tr>
<td>Protopanaxadiol</td>
<td></td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

As shown in the above Table 2, ginsenoside Rg3 content in red ginseng (obtained by steaming) was significantly increased in comparison with that of white ginseng, and in the case of said ginseng being fermented with lactic acid bacteria or intestinal bacteria, Compound K content was increased. Further, in the case of red ginseng, the content of ginsenoside Rh2 (metabolized ginsenoside Rg3) was significantly increased.
Experimental Example 1: Scratching Behavior Experiment

Scratching behavior experiment was conducted in accordance with the Sugimoto method (Eur. J. Pharmacol., 351, 1-5, 1998). Prior to the experiment, a group of five (5) rats consisting of BALB/c rats for an experimental animal model (Compound 48/80, Serotonin and Substance P) and ICR rats (an experimental animal model for histamine-induced itch) was left in a box (24x22x24cm) for observation for ten minutes. The hair on the rear neck was removed, and by using 29-gauge needle, itch-inducing agent (50 µg of Compound 48/80, Sigma Chemical Corp., USA), 100 µg of histamine (Sigma, USA), 300 µg of serotonin (Sigma Chemical Corp., USA) or 100 µg of Substance P (Sigma Chemical Corp., USA) were injected into the blood of each rat (for a normal control group, physiological saline solution was injected). Then, they were separated and put individually in a box and taped for one hour under an unmanned condition with 8-mm video (SV-K80, Samsung) to observe the results. Only the rats' scratching of the injected area with a rear leg was considered as a scratching behavior. To evaluate the efficacy of ginseng extracts and saponin derivatives isolated therefrom, experimental materials were intraperitoneally administered 1 hour before the injection of the itch-inducing agent, or
orally administered 6 hour before that. Each group consisted of five rats.

The results of the experiment were shown in Table 3 below.

<table>
<thead>
<tr>
<th>Samples</th>
<th>Content $s$ (mg/kg)</th>
<th>Oral administration</th>
<th>Intraperitoneal administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Induction by Compound 48/80</td>
<td>Induction by Compound 48/80</td>
</tr>
<tr>
<td>Example sample 1</td>
<td>50</td>
<td>34</td>
<td>-</td>
</tr>
<tr>
<td>Example sample 2</td>
<td>50</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Example sample 3</td>
<td>50</td>
<td>34</td>
<td>-</td>
</tr>
<tr>
<td>Example sample 4</td>
<td>50</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>Example sample 5</td>
<td>50</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside Rb1</td>
<td>10</td>
<td>28</td>
<td>55</td>
</tr>
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34
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<tr>
<th></th>
<th>10</th>
<th>30</th>
<th>48</th>
<th>40</th>
<th>38</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsenoside Rb2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginsenoside Re</td>
<td>10</td>
<td>26</td>
<td>51</td>
<td>41</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>10</td>
<td>30</td>
<td>63</td>
<td>51</td>
<td>48</td>
<td>-</td>
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<tr>
<td>Ginsenoside Rf</td>
<td>10</td>
<td>31</td>
<td>65</td>
<td>59</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside Rg3</td>
<td>10</td>
<td>15</td>
<td>70</td>
<td>68</td>
<td>89</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside F1</td>
<td>10</td>
<td>22</td>
<td>68</td>
<td>65</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside Rh2</td>
<td>10</td>
<td>29</td>
<td>60</td>
<td>58</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Ginsenoside Rh1</td>
<td>10</td>
<td>27</td>
<td>55</td>
<td>58</td>
<td>62</td>
<td>-</td>
</tr>
<tr>
<td>Compound K</td>
<td>10</td>
<td>41</td>
<td>73</td>
<td>74</td>
<td>93</td>
<td>77</td>
</tr>
<tr>
<td>Protopanaxadiol</td>
<td>10</td>
<td>22</td>
<td>45</td>
<td>35</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Azelnatine (positive control group)</td>
<td>5</td>
<td>45</td>
<td>65</td>
<td>75</td>
<td>47</td>
<td>77</td>
</tr>
</tbody>
</table>

As shown in the above Table 3, most of the ginseng saponins showed anti-itch effects and among them, Compound K and ferment derivatives of ginseng showed superior
effects. Among saponins, Compound K showed the best effects. Hence, it is confirmed that ginseng extracts and saponin derivatives is dated therefrom are effective in the treatment of scratching disease (pruritus; itch).

Experimental example 2: Inhibition of capillary vascular permeability

It is known that capillary vascular permeability is increased around itch induced areas, and therefore this experiment is carried out to see whether the extracts of the present invention are effective in inhibiting the vascular permeability induced by various compounds.

With a group of five rats (the same animals as in the previous experiment), the vascular permeability experiment with compound 48/80 was carried out in accordance with the Sugimoto Method (Eur. J. Pharmacol., 351, 1-5, 1998). That is, 50 µg of compound 48/80 was intradermally injected into the rear neck, 0.2 mL of 1% Evans blue solution (Sigma Chemical Corp., USA) was administered into a tail vein, and then an hour later, all the rats were killed. The area where Compound 48/80 had been administered was incised and soaked in 1 mL of 1N KOH, and then reacted at
the temperature of 37°C for 24 hours. Then, it was mixed with 4 ml of a mixed solution of 0.6N phosphoric acid-acetone (5:13) and subjected to centrifugal separation at 3000rpm for 15 minutes. The supernatant was taken and the absorbance thereof was measured at 620nm. The drugs used were the same as in the scratching experiment. The results were shown in Table 4 below.

[Table 4]

<table>
<thead>
<tr>
<th>Samples</th>
<th>Amounts (mg/kg)</th>
<th>Oral administration</th>
<th>intraperitoneal administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inducement by compound 48/80</td>
<td>Inducement by compound 48/80</td>
</tr>
<tr>
<td>Example sample 1</td>
<td>50</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Example sample 2</td>
<td>50</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Example sample 3</td>
<td>50</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Example sample 4</td>
<td>50</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside Rb1</td>
<td>50</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>Compound</td>
<td>10</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Ginsenoside de Rb2</td>
<td>10</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Ginsenoside de Re</td>
<td>10</td>
<td>26</td>
<td>47</td>
</tr>
<tr>
<td>Ginsenoside de Rg1</td>
<td>10</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td>Ginsenoside de Rf</td>
<td>10</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside de Rg3</td>
<td>10</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside de Rf1</td>
<td>10</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Ginsenoside de Rh2</td>
<td>10</td>
<td>35</td>
<td>61</td>
</tr>
<tr>
<td>Ginsenoside Rh1</td>
<td>10</td>
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</tr>
<tr>
<td>Compound K</td>
<td>10</td>
<td>26</td>
<td>45</td>
</tr>
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<td>Protopanaxadiol</td>
<td>10</td>
<td>35</td>
<td>63</td>
</tr>
<tr>
<td>Azelastine (Positive control group)</td>
<td>10</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-</td>
<td>65</td>
</tr>
</tbody>
</table>

In the above table, the Inhibition Rates were
calculated as follows.

\[
\text{Inhibition Rate (\%)} = \left\{1 - \frac{\text{absorbance on the area treated with extracts according to the present invention and Compound 48/80 (or histamine)}}{\text{absorbance on the area not treated with Compound 48/80 (or histamine)}}\right\} \times 100
\]

As shown in the above Table 4, as a result, whether orally administered or intraperitoneal administered, the capillary vascular permeability had been inhibited. In particular, Compound K showed superior effects, and so do ginseng and ferments. This efficacy was good for the inhibition of itch.

Hereinafter, examples of pharmaceutical preparations according to the present invention for the prevention or treatment of scratching disease are specifically explained, but it should be understood that the present invention is not limited to them.
Preparation Example 1. Preparation of Powdered Medicine

In accordance with a preparation method for powdered medicine in the provisions of pharmacopoeia, a bag can contain the following components as directed below:

Any one kind of the dried powders of Examples 1 to 4 ...

50mg

Lactose.................................................100 mg
Talc..................................................100 mg

Preparation Example 2. Preparation of Table

In accordance with a preparation method for tablets in the provisions of pharmacopoeia, a tablet can contain the following components as directed below:

*100 any one kind of the dried powder of Examples 1 to 4...

4...50mg

Corn starch........................................100 mg
Lactose.........................................100mg
Magnesium stearate .........................2mg
Preparation Example 3. Preparation of Capsule

In accordance with a preparation method for capsules in the provisions of pharmacopoeia, a capsule can contain the following components as directed below:

Any one kind of the dried powder of Examples 1 to 4 ..........50mg

Corn starch..................................................100 mg

Lactose.......................................................100mg

Magnesium stearate ..................................2mg

Preparation Example 4. Preparation of Liquid Medicine

In accordance with a preparation method for liquid medicine in the provisions of pharmacopoeia, 100ml of liquid medicine can contain the following components as directed below:

Any one dried powder of Examples 1 to 4 ... 50mg

Isomeric sugar.............................................10g

Mannitol......................................................5g

Distilled water.............................................proper quantity
Preparation Example 5. Preparation of Soap

In accordance with a general manufacturing method, soap containing the below content of each component is prepared.

Any one kind of the dried powder of Examples 1 to 4.....0.05 - 2mg
Palm Oil (and/or other Extra Oil).......................... 0.100g
NaOH or KOH..................................................... 0.15g (20g)
Distilled water.................................................. proper quantity

Also, a health beverage can be prepared with the following method.

0.1-80% of any one kind of the dried powder of Examples 1 to 4; 5-10% of sugar; 0.05-0.3% of citric acid; 0.005-0.02% of caramel; and 0.1-1% of vitamin C were mixed with 79-94% of distilled water to obtain a syrup, and said syrup was sterilized at a temperature of 85-98°C for about 20-180 seconds, mixed with cold water in the ratio of 1: 4. Then, 0.5-0.82% of carbon dioxide was inserted to finally obtain carbonated beverage containing specially processed dried ginseng extracts.
Supplements such as liquid-phase fructose (0.5%), oligosaccharide (2%), sugar (2%), culinary salt (0.5%) and water (75%) were homogeneously mixed with dried powder of Example 1, instantly sterilized, and then filled in a bottle or a polyethylene terephthalate to thereby prepare a health beverage.

The above compositional ratios examples of preferable ratios and thus, they could be modified as needed pursuant to local or ethnic preferences.

Such modifications are not to be considered as a departure form the spirit and scope of the present invention, and it would be obvious to the skilled person in the art that such modifications are intended to be included within the scope of the following claims.

As reviewed above, the composition from the present invention contains at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom as effective components, thereby being used as a composition for the prevention or treatment of scratching
disease.
What is claimed is:

1. A composition for preventing or treating scratching diseases (pruritus) containing at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom as effective components.

2. The composition for preventing or treating scratching diseases according to claim 1, wherein the ginseng saponin derivatives are at least one ginseng saponin derivatives selected from the group consisting of panaxytriol, panaxydol, panaxyanol, ginsenoside Rc, ginsenoside Rb1, Rb2, ginsenoside Rg3, compound K, ginsenoside Rh2, 20(R)-ginsenoside Rh2, 20(R)-protopanaxadiol, 20(S)-ginsenoside Rh2, 20(S)-protopanaxadiol, ginsenoside Rh1, 20(S)-protopanaxatriol and ginsenoside Rg3.

3. The composition for preventing or treating scratching diseases according to claim 1, wherein the lactic-acid bacteria used for lactic acid bacteria fermentation of ginseng or red ginseng extract is Bifidobacterium genus or Lactobacillus genus.

4. The composition for preventing or treating scratching diseases according to claim 1, wherein the
intestinal bacteria used for intestinal bacteria fermentation of ginseng or red ginseng extract is selected from the group consisting of Bacterioides genus, Fusobacterium genus, Eubacterium genus, and mixed microbes which are normal microflora in the intestine of human or mammal.

5. A method of preventing or treating scratching diseases comprising administering at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom.

6. A use of at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom for manufacturing a medicament for preventing or treating scratching diseases.

7. A pharmaceutical composition comprising at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom, and pharmaceutically acceptable excipients, carriers or
transporting agents.

8. A health care food comprising at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic-acid ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom, and sitologically acceptable additives.

9. A cosmetics comprising at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom, and cosmetically acceptable exipients, carriers or transporting agents.

10. A soap comprising at least one ginseng extract selected from the group consisting of ginseng or red ginseng extract, its lactic acid bacteria ferment and its intestinal bacteria ferment, or ginseng saponin derivatives isolated therefrom.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2005/001970

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 35/78
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 35/78, A23L 1/29, A61K 7/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubMed on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>JP 2003-238424 A (IL HWA CO., LTD.), 27 August 2003 See entire document</td>
<td>1-4, 6-10</td>
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<tr>
<td>X</td>
<td>WO 2004/050892 A1 (HONGRIM TRADING CO., LTD.), 17 June 2004 See entire document</td>
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<td>A</td>
<td>JP 11-236329 A (MEJI MILK PROD. CO., LTD.), 31 August 1999 See entire document</td>
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<td>A</td>
<td>KR 84-000561 B1 (PACIFIC CHEM. CO., LTD.), 23 April 1984 See entire document</td>
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<td>A</td>
<td>US 6630176 B2 (MOUNT SINAI SCHOOL OF MEDICINE OF NEW YORK UNIVERSITY), 07 October 2003 See entire document</td>
<td>1-4, 6-10</td>
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</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or the theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
11 OCTOBER 2005 (11.10.2005)

Date of mailing of the international search report
11 OCTOBER 2005 (11.10.2005)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
YE0, Ho Sup
Telephone No. 82-42-481-5627

Form PCT/ISA/210 (second sheet) (April 2005)
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 5 because they relate to subject matter not required to be searched by this Authority, namely:
   - Claim 5 is directed to a method for treatment of the human or animal body by therapy, and thus relates to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) and Rule 39.1(iv) PCT.

2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- i) Claims 1-4 and 6-7 are directed to a pharmaceutical composition.
- ii) Claim 8 is directed to a health care food.
- iii) Claims 9-10 are directed to a cosmetic or soap composition.

Although the abovementioned claims are relevant to the composition comprising the same active ingredient, there is no technical relationship among a pharmaceutical composition, a health care food and a cosmetic composition.

Hence, the application contains the three separate groups of inventions not so linked as to form a single general inventive concept (PCT Rule 13.1).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☑ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
<table>
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<th>Category</th>
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<th>Relevant to claim No.</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>HASEGAWA, H. et al. 'Main ginseng saponin metabolites formed by intestinal bacteria' In; Planta Med. 1996; 62(5): 453-7</td>
<td>1-4, 6-10</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
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