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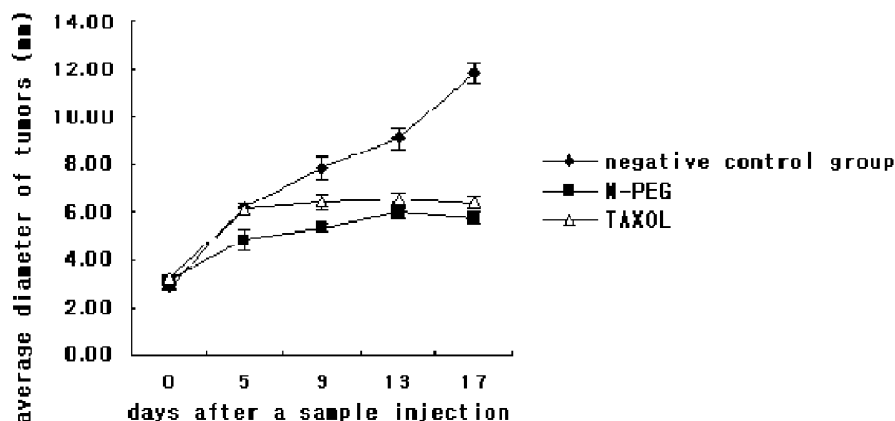
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[Continued on next page]

(54) Title: MONOMETHYLPHYTOSPHINGOSINE- POLYETHYLENEGLY COL AND THE COMPOSITION FOR ANTI-CANCER CONTAINING THE SAME



(57) Abstract: Disclosed are a monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative formed by combining monomethylphytosphingosine (MMPS), which is a derivative of sphingolipid, with polyethyleneglycol (PEG) or a pharmaceutically acceptable salt thereof and a composition containing the same. The compound inhibits a growth of tumor xenografted to the mammal, thereby treating or preventing a cancer or a cancer-related disease. In addition, it is possible to inhibit an activity of promoting a cell proliferation, thereby treating or preventing a hyper-proliferative disease such as a cancer and psoriasis. Further, a solubility of the monomethylphytosphingosine is improved and a toxicity thereof influencing on the human body is reduced, thereby remarkably expanding the application ranges thereof.



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Description

MONOMETHYLPHYTOSPHINGOSINE-POLYETHYLENEGLYCOL AND THE COMPOSITION FOR ANTI-CANCER CONTAINING THE SAME

Technical Field

- [1] The present invention relates to a derivative of sphingolipid having an anti-cancer activity and a composition containing the same, and more particularly to a monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative formed by combining monomethylphytosphingosine (MMPS), which is a derivative of sphingolipid, with polyethyleneglycol (PEG) or a pharmaceutically acceptable salt thereof and a composition containing the same.

[2]

Background Art

- [3] Sphingolipid was firstly found by Thudichum in 1884 and named as a sphinx like substance. It was known as a substance playing a substantial role in life phenomena as well as regulating cell growth, proliferation and differentiation.
- [4] The sphingolipid in a human body has sphingosine, phytosphingosine or sphinganine backbones and 300 or more kinds of derivatives including ceramide having fatty acids connected to the backbones.
- [5] The sphingolipid is a main ingredient constituting a cell membrane together with phospholipid and has polar and non-polar parts. Ceramide having a fatty acid connected to sphingolipid is known as a substance playing an important role in causing various action mechanisms occurring in a cell. In particular, it takes part in a cell proliferation, a cell differentiation, a temporary growth arrest of the cell proliferation and an apoptosis.
- [6] Since 1990's, functions of the sphingolipid have been analyzed in earnest. In particular, the researches thereof have been actively performed as a protein kinase inhibiting effect of sphingosine was validated by Hannun and Bell, etc. In addition, as it was found that an important life phenomenon such as the cell differentiation, growth, aging and death is regulated by ceramide, it was become a core of a biology research.
- [7] The ceramide is a substance causing an apoptosis which is an importance mechanism for a cancer treatment and thus development of an anti-cancer drug is focused on the ceramide. It is analyzed that many anti-cancer drugs, which are being currently used or developed, influence on a biosynthesis pathway of the ceramide and thus exhibit their effects.
- [8] As a treatment for killing a cancer cell, ceramide and ceramide derivative and

analog are directly treated to the cancer cell or a substance inducing or starting a de novo synthesis of ceramide may be used as an anti-cancer drug.

- [9] Accordingly, since a substance regulating an activity of enzyme participating in biosynthesis of ceramide and sphingolipid is highly possibly to be developed as an anti-cancer drug, it is recently taken intensive interests. Serine palmitoyl transferase (SPT), ceramidase, sphingomyelinase (SMase), gluco-sylceramide (GlcCer) synthase and sphingosine kinase, etc. are enzymes participating in synthesis and hydrolysis of ceramide, and substances for activating and inhibiting such enzymes suggest a possibility of properly regulating a content of ceramide in a cancer cell and thus inducing an apoptosis of the cancer cell.
- [10] Researches on substances regulating a content of ceramide in a cell can be confined to developments of derivatives and analogs of sphingolipid and ceramide and include many kinds of substances, for example, functional fatty acids, vitamins, androgen and ROS (reactive oxygen species: hydroxyperoxide, nitric oxide releasing compound) influencing on biosynthesis of sphingolipid, and substances influencing on a glutathione (GSH) level and a lecithin level.
- [11] Among them, P-drug, which has been actively researched as an anti-cancer drug in recent years, is a ceramide analog of aminoalcohols. PDMP (D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol) among them is an initial synthesis substance which is most developed and exhibits an excellent effect as an inhibitor of a synthesis of GlcCer (glucosyl ceramide) greatly influencing on a cell cycle. PPMP (D-threo-1-phenyl-2-palmitoylamino-3-morpholino-1-propanol) having a better effect than PDMP is a homolog having a longer chain and PPPP (P4D-threo-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol) is also an analog exhibiting an inhibitory effect higher than PDMP. The P-drug is expected to exhibit an anti-cancer effect for a general cancer cell and to inhibit a synthesis of GlcCer relating to tolerance to the anti-cancer drug, thereby contributing to a prevention of drug resistance.
- [12] In addition, B13 or N-oleoylethanolamine, which are ceramidase inhibitors, is also a ceramide analog and inhibits a decomposition of the ceramide to induce a death of the cancer cell. Further, there are ceramide biosynthesis inhibitors having a structure similar to those of sphingolipid and ceramide, such as FTY-720, fumonisins and myriocin, etc.
- [13] There are many substances which have been already used as an anti-cancer drug, among the substances participating in the ceramide biosynthesis. Vincristine, gemcitabine, camptothecin, homocamptothecin, irinotecan, etc. are representative examples, most of which promote an activity of SMase. However, since GlcCer and sphingosine 1-phosphate (S1P) produced from ceramide promote a cancer cell growth,

it is expected that a development of a selective inhibitor of GlcCer synthase, ceramidase or sphingosine kinase (SPHK) will be an efficient treatment strategy for cancer. In particular, the SPHK inhibitor is a development target for a new anti-cancer drug and thus being recently researched.

- [14] As a new anti-cancer target, many concerns have been recently focused on dimethylsphingosine (DMS) produced by methylation of sphingosine and safinol which is an isomer of sphinganine, which are known as a SPHK inhibitor. In fact, according to a study of a M.D. Anderson cancer research institute, the DMS was shown to have an efficacy for an acute leucosis exhibiting a drug resistance and a possibility of being developed into an anti-cancer drug was confirmed. In addition, researches on a specific structure capable of regulating contents of sphingolipid and ceramide in a cell by using such substances have been actively progressed.
- [15] In addition, various substances have been suggested to increase practical uses of sphingolipid and ceramide. In particular, since ceramide having polyethylene glycol connected thereto renders a liposome be easily formed and increases a circulation lifetime, researches on such substances and a composition for liposome formation are being progressed.
- [16] In the mean time, since the sphingolipid has a poor solubility, there are many restraints to apply it to various formulations.
- [17] The polyethylene glycol above mentioned is a substance having a structure of $\text{HO}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2\text{-OH}$, and often used in foods or cosmetics. In addition, since it retards decomposition of an active ingredient, it has been much used in prescription of drug. The polyethylene glycol is a substance suitable for such purposes since it is a non-toxic polymer, has a good solubility and no antigenicity in a human body and is easily removed in the body. Since the polyethylene glycol has a hydroxyl group at both ends thereof, monomethoxy polyethylene glycol $(\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2\text{-OH})$ having one end blocked is much used in PEGylation and its molecular weight is used up to 30,000 Daltons. In order to connect monomethoxy polyethylene glycol to a drug, a hydroxyl group at one end having no methoxy connected thereto is activated and connected using various chemicals.

[18]

Disclosure of Invention

Technical Problem

- [19] Accordingly, the inventors applied various changes of a functional group to a basic structure of sphingolipid and thus synthesized derivatives having a new structure, an anti-cancer efficacy and an improved solubility through a medical chemistry molecule design. As a result of that, it was validated that monomethylphytosphingosine-

polyethyleneglycol (MMPS-PEG) exhibits an excellent anti-cancer efficacy, an improved solubility and an effect of reducing a toxicity influencing on the human body.

- [20] Accordingly, the present invention has been made to solve the above-mentioned problems occurring in the prior art. The object of the present invention is to inhibit a growth of tumor xenografted to a mammal using a derivative of sphingolipid, i.e., a monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative formed by combining monomethylphytosphingosine (MMPS) with polyethyleneglycol (PEG), thereby treating or preventing a cancer or a cancer-related disease. Another object of the invention is to inhibit an activity of promoting a cell proliferation, thereby treating or preventing a hyper-proliferative disease such as a cancer and psoriasis. Accordingly, the object of the invention is to provide a tumor inhibiting composition, an anti-cancer composition or composition for treating or preventing a hyper-proliferative disease, which compositions have the above-mentioned efficacies.

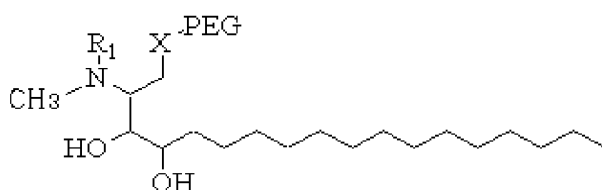
[21]

Technical Solution

- [22] In order to accomplish the objects, there is provided a monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative formed by combining monomethylphytosphingosine (MMPS) with polyethyleneglycol (PEG) and having a following chemical formula 1 or a pharmaceutically acceptable salt thereof and a composition containing the same.

[23]

[24] ChemistryFigure 1



[25]

- [26] wherein R_1 is independently hydrogen, alkyl group of C_{1-40} , alkenyl group of C_{1-40} , alkynyl group of C_{1-40} , acyl group or aryl group, in a case of acyl group (COR_2), R_2 is alkyl group, alkenyl group, alkynyl group or aryl group, a substituent X is a medium used to combine with sphingolipid and $-NR_3-$, $-O-$, $-S-$, or $X_1-alk-X_2$, R_3 is hydrogen, alkyl group of C_{1-6} , acyl group or aryl group, X_1 and X_2 are independently amino group, amido group, carboxyl group, carbamate group, carbonyl group, urea or phosphoro, and alk is alkylene of C_{1-6} .

- [27] In the monomethylphytosphingosine-polyethyleneglycol derivative of the invention,

the polyethyleneglycol has a molecular weight of 550 ~ 10,000, more preferably, 750 ~ 5,000 and an end replaced with methoxy.

[28] A representative example of the monomethylphytosphingosine-polyethyleneglycol derivatives according to the invention is one wherein R_1 is independently hydrogen, alkyl group or acyl group, X is succinate and the polyethyleneglycol has a molecular weight of 750 ~ 5,000 and an end replaced with methoxy group.

[29] According to the invention, there is provided a tumor inhibiting composition containing the monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative or a pharmaceutically acceptable salt thereof as an effective ingredient.

[30] In addition, the tumor inhibiting composition is used to treat or prevent a cancer or cancer-related disease.

[31] According to the invention, there is provided an anti-cancer composition for treating or preventing a cancer containing the monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative or a pharmaceutically acceptable salt thereof as an effective ingredient.

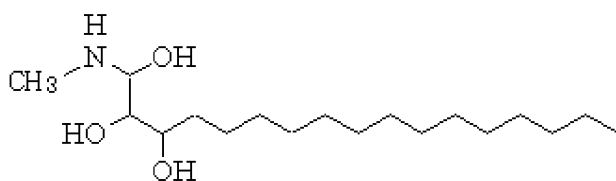
[32] According to the invention, there is provided a composition for treating or preventing a hyper-proliferative disease containing the monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative or a pharmaceutically acceptable salt thereof as an effective ingredient.

[33] In addition, the hyper-proliferative disease is psoriasis.

[34] The composition of the invention containing the monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative or a pharmaceutically acceptable salt thereof can be used in a medicine. The salt is not specifically limited if it is pharmaceutically acceptable. For example, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrofluoric acid, hydrobromic acid, formic acid, acetic acid, tartaric acid, lactic acid, citric acid, fumaric acid, maleic acid, succinic acid, methane sulfonic acid, benzene sulfonic acid, toluene sulfonic acid and naphthalene sulfonic acid, etc. can be used.

[35] The monomethylphytosphingosine-polyethyleneglycol derivative having the chemical formula 1 according to the invention can be prepared by reacting monomethylphytosphingosine having a following chemical formula 2 with polyethyleneglycol which is activated in advance in a solvent under presence of catalyst.

[36] Chemistry Figure 2



[37]

Advantageous Effects

[38] The MMPS-PEG derivative or the pharmaceutically acceptable salt thereof according to the invention highly inhibits a growth of tumor xenografted to the mammal, thereby treating or preventing a cancer or a cancer-related disease. In addition, according to the invention, it is possible to inhibit an activity of promoting a cell proliferation, thereby treating or preventing a hyper-proliferative disease such as a cancer and psoriasis. Further, a solubility of the monomethylphosphatidylcholine is improved and a toxicity thereof influencing on the human body is reduced, thereby remarkably expanding the application ranges thereof. Accordingly, the composition containing the same can be efficiently used as a tumor inhibiting composition, an anti-cancer composition for treating or preventing a cancer or a cancer-related disease or a composition for treating or preventing a hyper-proliferative disease.

[39]

Brief Description of the Drawings

[40] FIG. 1 is a graph showing an anti-cancer efficacy of a MMPS-PEG derivative in a nude mouse; and

[41] FIG. 2 is a graph showing a survival rate of a nude mouse having a tumor grafted thereto which is treated with the MMPS-PEG derivative.

[42]

Best Mode for Carrying Out the Invention

[43] Hereinafter, the present invention will be more specifically described.

[44] A detailed description of a method of manufacturing the monomethylphosphatidylcholine-polyethyleneglycol derivative having the chemical formula 1 is as follows. Firstly, polyethyleneglycol is activated. Succinic anhydride is added to the polyethyleneglycol under presence of an organic solvent, thereby converting an alcohol group into a carboxyl group. An acid part of the polyethyleneglycol having carboxyl group replaced is activated using triethylamine and p-toluenesulfonylchloride and then a small amount of monomethylphosphatidylcholine is added to the activated solution a small amount by a small amount, thereby completing a 24 hours reaction under warming conditions.

[45] The compound having the chemical formula 1 prepared as described above is

extracted using an organic solvent such as chloroform or a mixed solution of chloroform and methanol and then purified with an adsorption chromatography by silica gel.

- [46] The purified monomethylphytosphingosine-polyethyleneglycol derivative can be used in a medicine as it is or in a form of pharmaceutically acceptable salt. The salt is not specifically limited if it is pharmaceutically acceptable. For example, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrofluoric acid, hydrobromic acid, formic acid, acetic acid, tartaric acid, lactic acid, citric acid, fumaric acid, maleic acid, succinic acid, methane sulfonic acid, benzene sulfonic acid, toluene sulfonic acid and naphthalene sulfonic acid, etc. can be used.
- [47] In the monomethylphytosphingosine-polyethyleneglycol derivative of the invention, the polyethyleneglycol has preferably a molecular weight of 550 ~ 10,000, more preferably 700 ~ 5,000. The range of the molecular weight is the most optimal range for achieving a purpose of combining the polyethyleneglycol.
- [48] In addition, a pharmaceutical composition containing the monomethylphytosphingosine-polyethyleneglycol derivative or the pharmaceutically acceptable salt thereof preferably contains 0.001 ~ 20 wt.% of the compound in a total composition. When the concentration is less than 0.001 wt.%, it is difficult to obtain the efficacy and when the concentration is more than 20 wt.%, it can cause an abnormality of a generative function.
- [49] It can be expected that the monomethylphytosphingosine-polyethyleneglycol derivative of the invention inhibits a growth of tumor grafted in a living mammal and has an increased solubility and a decreased toxicity.
- [50] The inventors measured an in vivo anti-cancer activity using a derivative of sphingolipid, i.e., the monomethylphytosphingosine-polyethyleneglycol derivative (MMPS-PEG) having the chemical formula 1 formed by combining monomethylphytosphingosine (MMPS) with polyethyleneglycol (PEG). Specifically, the anti-cancer efficacy of the monomethylphytosphingosine-polyethyleneglycol was measured by xenografting human breast cancer cells, i.e., MDA-MB-231 to a nude mouse. As a result of that, it was validated that the compound exhibited an anti-cancer efficacy almost similar to that of TAXOL which is an existing anti-cancer drug.
- [51] In addition, it was also validated a solubility increase and a decrease of toxicity influencing on a human body regarding the compound.
- [52] According to the invention, a pharmaceutical composition containing the monomethylphytosphingosine-polyethyleneglycol derivative and the pharmaceutically acceptable salt thereof may further comprise proper carrier, excipient and diluent typically used to prepare the pharmaceutical composition.
- [53] The compound of the invention can be pharmaceutically administrated in a form of

a pharmaceutically acceptable salt thereof. Further, it can be administrated solely or in conjunction with and in a proper combination with other pharmaceutically acceptable active compounds.

[54] The pharmaceutical composition containing the compound of the invention can be used in forms of oral formulation such as acida, granulum, tablet, capsule, suspension, emulsion, syrup and aerosol, external preparations such as ointment and cream, suppository and sterilizing injection solution according to typical methods. Further, it can be formulated in any forms suitable for pharmaceutical preparations.

[55] Although a preferable dosage of the compound according to the invention varies with ages, sexes, weights, symptoms and degrees of diseases of administration subjects, drug forms, administration routes and administration periods, it can be properly selected by a skilled person in the art. However, considering a preferable efficacy, it is preferred that the compound of the invention is administrated in an amount of 0.001 ~ 1000 mg/kg per a day. The administration can be performed one time or many times per a day. In addition, the dosage can be increased or decreased according to the ages, sexes, weights, degrees of diseases and administration routes, etc. Accordingly, the dosage does not limit a scope of the invention in any way.

[56] The compound of the invention can be administrated to a mammal such as a rat, a mouse, a domestic animal and a human through various routes, for example, non-oral and oral administrations. All types of the administration can be expected. For instance, it can be administrated with oral, rectum or vein, muscle, hypodermic, and intrauterine dura mater or intracerebroventricular injections.

[57] Since the monomethylphytosphingosine-polyethyleneglycol derivative and the salt containing the same according to the invention have little serious toxicity and side effect, they can be safely used for a prevention purpose for a long time.

[58]

Mode for the Invention

[59] Hereinafter, the invention will be more specifically described with reference to examples and experimental examples. However, it should be noted that a scope of the invention is not limited to the examples in any way.

[60]

[61] **Example 1: synthesis of monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative**

[62] 5.0 g of methoxypolyethyleneglycol (0.0067 mole) was dissolved in pyridine solvent under nitrogen gas and 6.67 g of succinic anhydride (0.067 mole) was slowly added to the solution. After that, the mixture was reacted for 24 hours under state that light was excluded. After the reaction was completed, the pyridine was converted into

a salt form by adjusting to pH 2 with an addition of hydrofluoric acid, and then extracted and removed by adding chloroform and water. At this time, an excess amount of succinic anhydride was extracted and removed as a water layer. 1 g of methoxypolyethyleneglycol-carboxyl acid (0.0011 mole) obtained through the above procedures was dissolved in dichloromethane solvent under nitrogen gas, a carboxyl group thereof was activated using 0.17 ml of triethylamine (0.0017 mole) and 2.11 g of p-toluenesulfonylchloride (0.011 mole), 0.22 g of N-methylphytyosphingosine (0.0011 mole) was slowly added, and then a reaction was progressed for 24 hours under warming conditions. After the reaction was completed, the reaction was stopped with distilled water extraction. Then, it was obtained the compound having the chemical formula 1 through an adsorption chromatography by silica gel. In addition, the succinate, which was introduced in the methoxypolyethyleneglycol by reacting with succinic anhydride, was confirmed with ^1H NMR (Avance 500, Bruker) (δ = 2.6 ppm, t, 4H). Finally, methylene (δ = 1.2 ppm, m, 48H) and (δ = 0.9 ppm, t, 6H) of monomethylphytyosphingosine, and ethoxy (δ = 3.6 ppm, m, 64H) and methoxy (δ = 3.3 ppm, s, 3H) of methoxypolyethyleneglycol were confirmed, and it was therefore confirmed that a monomethylphytyosphingosine-polyethyleneglycol (MMPS-PEG) derivative was synthesized, which is a derivative of the invention formed by combining methoxypolyethyleneglycol with monomethylphytyosphingosine.

[63]

[64] **Experimental example 1: anti-cancer efficacy of MMPS-PEG derivative in an experimental animal (in vivo efficacy evaluation of MMPS)**

[65] In order to validate an anti-cancer efficacy of the MMPS-PEG derivative prepared according to the example 1, a following experiment as a pre-clinical experiment was performed using a nude mouse as an experimental animal. At this time, experimental animals exhibiting a weight increase and an abnormality in a general symptom during the experiment period were excluded from an experiment result.

[66] Firstly, a sufficient amount of human breast cancer cell line, i.e., MDA-MB-231 (obtained from Korea Institute of Radiological and Medical Sciences, Gongneung-dong, Seoul) was cultivated and about 10^6 of cells were injected into nude mice (6-week of age, about 20 g, 6 (six) per group, SLC, Japan). After few days, when a size of tumor was increased to about 3 mm, the MMPS-PEG derivative of the Example 1 was injected in the nude mouse (125 mg/kg, three times of intraperitoneal administration) and fractionation-injection conditions of test materials were set while measuring the tumor size. In addition, regarding evaluations of anti-cancer efficacy, the tumor size was measured using calipers per day and a survival rate of the treatment group was evaluated. At this time, phosphate buffered solution (PBS) was used as a negative control group and TAXOL was used as a positive control group in the

experiment.

[67] As a result of that, as can be seen from Fig. 1, MMPS-PEG derivative (125 mg/kg, three times of intraperitoneal administration) exhibited an anti-cancer efficacy almost similar to that of TAXOL (30 mg/kg, three times of intraperitoneal administration) which is an anti-cancer drug currently used in clinic, although there is a difference between concentrations exhibiting the efficacies.

[68] In addition, the survival rates are shown in Fig. 2. As can be seen from Fig. 2, all mouses of the negative control group were dead on 45 days, but 50% of the group injected with the MMPS-PEG derivative was survived.

[69] Formulation examples of the composition are set forth as follows. However, it should be noted that the examples are given only to illustrate the invention, not to limit it.

[70]

[71] **<Formulation example 1: MMPS-PEG derivative 2% cream>**

[72] Table 1

Ingredients	Contents (wt.%)
MMPS-PEG derivative of Example 1	2.0%
Propylene glycol	20.0%
Stearyl alcohol	6.5%
Cetyl alcohol	3.5%
Sorbitan monostearate	3.0%
Polysorbate 60	2.0%
Isopropyl myristate	1.0%
Anhydrous sodium sulfite	0.2%
Polysorbate 80	0.1%
Purified water	61.7%

[73]

[74] Stearyl alcohol, cetyl alcohol, sorbitan monostearate and isopropyl myristate were introduced in a double-walled receptacle and then the mixture was heated until it was completely dissolved. The mixture was added to a mixture of purified water, propylene glycol and polysorbate 60 separately prepared using a liquid homogenizer at 70~75 °C. The produced emulsion was continuously mixed and cooled to below 20 °C. Subsequently, the solution of MMPS-PEG derivative, polysorbate 80 and purified water and the anhydrous sodium sulfite solution in the purified water were added to the emulsion while continuously mixing the solutions. The cream was homogenized and

filled in a proper tube.

[75] <Formulation example 2: MMPS-PEG derivative 2% local gel>

[76] Table 2

Ingredients	Contents (wt.%)
MMPS-PEG derivative of Example 1	2.0%
Propylene glycol	4.0%
Hydroxypropyl b-cyclodextrin	25.0%
Ethyl alcohol 95% (v/v)	4.0%
Carrageenan PJ	1.0%

[77]

[78] A proper amount of hydrochloric acid was added to be a solution. A proper amount of sodium hydroxide was added to be pH 6.0. A proper amount of purified water was added to be 100 mg.

[79] MMPS-PEG derivative was added to a solution of hydroxypropyl b-cyclodextrin in purified water while stirring it. Hydrochloric acid was added to be a solution and then sodium hydroxide was added to be pH 6.0. This solution was added to a dispersion solution of carrageenan PJ in propylene glycol while mixing it. The mixture was heated to 50 °C while slowly mixing, and added with ethyl alcohol and then cooled to about 35 °C. A remaining amount of purified water was added to the mixture and then the mixture was mixed to be homogeneous.

[80]

[81] <Formulation example 3: MMPS-PEG derivative nano-dispersion solution>

[82] Table 3

MMPS-PEG derivative nano-dispersion solution inversion phase

Ingredients	Contents (wt.%)
MMPS-PEG derivative of Example 1	36.6%
Phosphatidyl choline	9.0%
Polysorbate 80	34.0%
Ethyl alcohol	7.4%
Migliol 812	13.0%

[83]

[84] Migliol 812, MMPS-PEG derivative and polysorbate 80 were mixed. Phosphatidyl choline was dissolved in ethanol and then added to the mixture to obtain a homogeneous clear liquid.

[85]

[86] Table 4

MMPS-PEG derivative nano-dispersion solution water phase

Ingredients	Contents (wt.%)
MMPS-PEG derivative of Example 1	2.0%
Phosphatidyl choline	0.49%
Polysorbate 80	1.86%
Ethyl alcohol	0.63%
Migliol 812	0.71%
Purified water	Added to be 100.0%

[87]

[88] A water phase containing MMPS-PEG derivative (for example, 94.54 g) was stirred and kept at 50 °C in a receptacle. A liquid nano-dispersion solution inversion phase (for example, 5.46 g) was stirred and added to the water phase.

[89]

Industrial Applicability

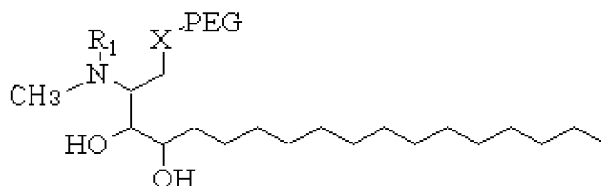
[90]

As described above, the MMPS-PEG derivative or the pharmaceutically acceptable salt thereof according to the invention highly inhibits a growth of tumor xenografted to the mammal, thereby treating or preventing a cancer or a cancer-related disease. In addition, according to the invention, it is possible to inhibit an activity of promoting a cell proliferation, thereby treating or preventing a hyper-proliferative disease such as a cancer and psoriasis. Further, a solubility of the monomethylphytosphingosine is improved and a toxicity thereof influencing on the human body is reduced, thereby remarkably expanding the application ranges thereof. Accordingly, the composition containing the same can be efficiently used as a tumor inhibiting composition, an anti-cancer composition for treating or preventing a cancer or a cancer-related disease or a composition for treating or preventing a hyper-proliferative disease.

Claims

- [1] A monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative having a following chemical formula 1 or a pharmaceutically acceptable salt thereof,

[Chemistry Figure 1]



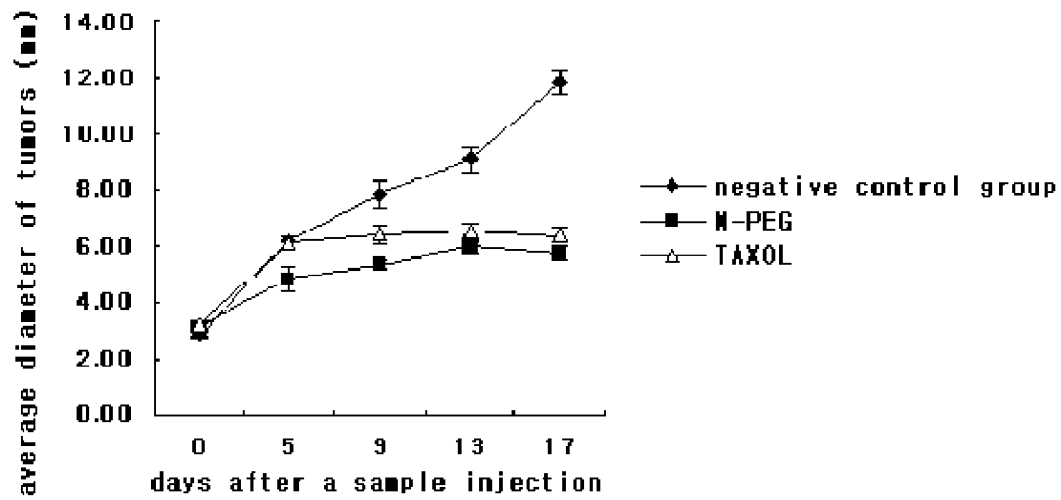
wherein R_1 is independently hydrogen, alkyl group of C_{1-40} , alkenyl group of C_{1-40} , alkynyl group of C_{1-40} , acyl group or aryl group,

in a case of acyl group (COR_2), R_2 is alkyl group, alkenyl group, alkynyl group or aryl group, and

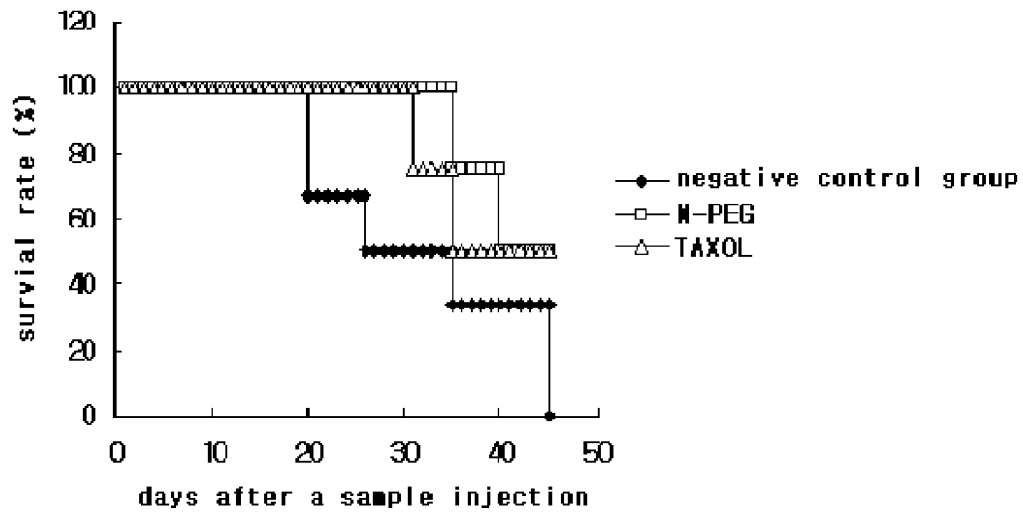
a substituent X is a medium used to combine with sphingolipid and $-NR_3$ -, $-O$ -, $-S$ -, or X_1 -alk- X_2 , R_3 is hydrogen, alkyl group of C_{1-6} , acyl group or aryl group, X_1 and X_2 are independently amino group, amido group, carboxyl group, carbamate group, carbonyl group, urea or phosphoro, and alk is alkylene of C_{1-6} .

- [2] A tumor inhibiting composition containing the monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative or the pharmaceutically acceptable salt thereof according to claim 1 as an effective ingredient.
- [3] An anti-cancer composition for treating or preventing a cancer or cancer-related disease containing the monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative or the pharmaceutically acceptable salt thereof according to claim 1 as an effective ingredient.
- [4] A composition for treating or preventing a hyper-proliferative disease containing the monomethylphytosphingosine-polyethyleneglycol (MMPS-PEG) derivative or the pharmaceutically acceptable salt thereof according to claim 1 as an effective ingredient.
- [5] The composition according to claim 4, wherein the hyper-proliferative disease is psoriasis.

[Fig. 1]



[Fig. 2]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2005/001438

A. CLASSIFICATION OF SUBJECT MATTER**IPC7 C07C 215/10**

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)

IPC7 C07C, A61K

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)
CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5820873 (THE UNIVERSITY OF BRITISH COLUMBIA) 13 OCTOBER 1998 See the claims	1-5
A	WO 03/101937 A1 (BUNDLE, DAVID, R.) 11 DECEMBER 2003 See the whole document	1-5
A	WO 03/92667 A1 (DOOSAN CO.) 13 NOVEMBER 2003 See the whole document	1-5
A	KR 03014780 A (CHARMZONE CO.) 20 FEBRUARY 2003 See the whole document	1-5
P, X	WO 04/54963 A1 (DOOSAN CO.) 1 JULY 2004 See the whole document -----End of documents-----	1-5



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

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"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 theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

18 AUGUST 2005 (18.08.2005)

Date of mailing of the international search report

22 AUGUST 2005 (22.08.2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2005/001438

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KR 03014780	20. 02. 2003	None	
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