Use of toosendanin or extracts of melia azedarach for the prevention or treatment of dementia

Abstract

translated from Spanish

A composition for use in the prevention or treatment of dementia comprising toosendanine represented by formula 1 or a pharmaceutically acceptable salt thereof as an active ingredient. **Formula**

Classifications

A61K31/568 Compounds containing cyclopenta[a]hydrophenanthrene ring systems; Derivatives thereof, e.g. steroids not substituted in position 17 beta by a carbon atom, e.g. estrane, estradiol substituted in positions 10 and 13 by a chain having at least one carbon atom, e.g. androstanes, e.g. testosterone

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Other languages

Spanish

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Description

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DESCRIPTION

Use of toosendanin or extracts of Melia azedarach for the prevention or treatment of dementia.

Technical Field 5

This application claims the priority and benefit of Korean Patent Application No. 10 - 2009 - 0054949, filed on June 19, 2009, which is incorporated herein by reference for all purposes as fully established therein.

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The present invention relates to the use of toosendanine or cinnamon extracts (Melia azedarach, Melia toosendan) for the prevention or treatment of dementia. More particularly, the present invention relates to a pharmaceutical composition for use in the prevention or treatment of dementia comprising toosendanine or a pharmaceutically acceptable salt thereof.

fifteen

Prior art

Dementia is a syndrome that progresses gradually over the long term, a serious disorder in the faculty of memory, concentration, language and recognition due to damage or loss of neurons, resulting in the loss of mental capacity and social activity. A representative disease that causes dementia 20 is Alzheimer's disease. Alzheimer's disease is divided into a sporadic type and a family type depending on its origin. The sporadic type of Alzheimer's disease, of unknown origin, occurs in 80 ~ 90% or more of patients with Alzheimer's disease, and occurs mainly in older people (after 65 years). The other type of Alzheimer's disease is mainly caused by a gene mutation, such as the amyloid precursor protein (hereinafter referred to as PPA), and presenilin (PS) - 25 1 and 2, and always occurs in young people. (before age 65). Alzheimer's symptoms are considered to be caused mainly by a beta amyloid (hereinafter referred to as Aβ) that forms a senile plaque outside the neurons of brain tissues, and a hyperphosphorylated Tau protein that forms a helical filament paired in the neurons It was revealed that Aβ is a protein formed by 40-42 amino acids, formed during the specific metabolism of the amino acid sequence of PPA by some 30 proteases, that is, β- and γ-secretases, causes neurotoxicity, synapse loss and inflammation to be added in itself (Cappari et al, Neurochem Res, 2008, 33: 526-532). In addition, it was reported that a Tau protein plays a role in maintaining the shape and structure of a cell by binding to microtubules, and a hyperphosphorylated Tau protein separates from the microtubules, destroys the microtubule, and forms neurofibrillar clews, inducing death. of neurons (Iqbal et al, Acta Neuropathol, 2009, published). It is known that the number of 35 patients suffering from Alzheimer's disease is approximately 26 million worldwide (in 2008), and the number is also estimated to reach 100 million or more by 2050 due to the increase in the population of old age (Carlsson, J Alz Dis, 2008, 15: 327-338). However, the development of a fundamental therapeutic agent has been carried out very slowly. Examples of currently available drugs include inhibitors of acetylcholinesterase activity (e.g., Aricept, Exelon, Reminyl) to fix the concentration of acetylcholine (memory-related neurotransmitter), and an NMDA receptor antagonist (e.g., Memantine) to inhibit a neuronal cell death caused by Ca2 +. However, these are only used to decrease the progress of symptoms. Therefore, it is required to urgently develop a therapeutic agent that shows a fundamental therapeutic effect.

Four. Five

Cinnamon (Melia azedarach, Melia toosendan) is classified in the Meliaceae family and Melia genus. Its canopy or bark is called Meliae cortex and its fruit is called Toosendan Fructus. They have been used primarily as anthelmintics since ancient times (in China), and also show antibacterial, diuretic, and antipyretic effects. Also, according to the annotations in Donguibogam (Book on traditional Korean medicine), they can be used for the treatment of scrotal hernia (inflammation or pain in the reproductive system / testicles, and urinary and fecal disorder). It was reported that the anthelmintic effect of Meliae cortex or Toosendan Fructus of melia azedarach is obtained by triterpenoid-based toosendanine (or azedarachina, C30H38O11, molecular weight 574, Wang and Yen, J Tradit Chin Med 1959, 262: 46-49) due to which toosendanin selectively inhibits the intake and differentiation of an insect (Zhang et al, Acta Northwe Uni Agriculture Sin, 1993, 21: 1-5). Apart from cinnamon, Cedrela sinensis is classified in the same Meliaceae 55 family that contains toosendanin. Its stem / bark of the stem that is, cedrelae cortex, is used as anthelmintic, antidiarrheal and therapeutic agents for shigellosis and leukorrhea.

In addition, it was reported that toosendanin induces neuronal differentiation (Tang et al, Neurosci Res, 2003, 45: 225-231) and apoptosis of cancer cells (Shi and Tang, Chin J Neurosci, 2004, 20: 461-462) . 60 Also, there are national and international patents related to the use of cinnamon, including cancer cell cytotoxicity (Registered Korean Patent No. 10-0112032), a whitening and anti-wrinkle effect (Registered Korean Patent No. 10-0345226, and registered US Patent No. 06,866,856), an insecticidal effect (Registered Korean Patent No. 10 - 0112657, and registered US Patent No. 06,372,239), and an allergy prevention effect (Registered Korean Patent No. 10 - 0750879 B1). A composition for the treatment against cancer is also described, which contains an extract of Melia leaves.

azedarach L. (U.S. Patent Application No. 4,563,496 A). However, there is no research on the effect of toosendanin on dementia.

Divulgation

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Technical problem

The inventors of the present invention investigated a new material for the treatment of dementia, and discovered that an extract of the cinnamon fruit (i.e., Toosendan Fructus) that includes toosendanine, and the toosendanin separated from the extract, facilitates the production of PPAα that It shows a protective effect of the neuron through the control of the metabolism of PPA, and inhibits the production of Aβ, thereby improving memory in an animal model of dementia. Later, this invention was completed based on the finding.

Accordingly, it is the object of the present invention to present the use of toosendanine or its pharmaceutically acceptable salt for the prevention or treatment of dementia.

Another object of the present invention is to present the use of a cinnamon extract for the prevention or treatment of dementia.

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Technical solution

To achieve an object of the present invention, the present invention has a pharmaceutical composition for use in the prevention or treatment of dementia, comprising toosendanine or a pharmaceutically acceptable salt thereof as an active ingredient. 25

To achieve another object of the present invention, the present invention presents a use of toosendanine or a pharmaceutically acceptable salt thereof for the preparation of an agent to prevent or treat dementia.

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To achieve another object of the present invention, the present invention presents a pharmaceutical composition for use in the prevention or treatment of dementia, comprising cinnamon extract (Melia azedarach or Melia toosendan) as active ingredient.

To achieve another object of the present invention, the present invention presents a use of cinnamon extract (Melia azedarach or Melia toosendan) for the preparation and treatment of dementia.

Hereinafter, the present invention will be described in detail.

The toosendanin used in the present invention represented by formula 1 is known to show an insecticidal effect, a cytotoxicity of cancer cells, and bleaching and anti-wrinkle effects, and also shows a dementia prevention / treatment effect. For the first time, the effect of toosendanin has been disclosed in the present invention.

[Formula 1] 45

image 1

C30H38O11 (molecular weight 574.62)

Dementia represents a disease that causes acquired cognitive dysfunction and personality changes, despite the normal intellectual level in the period of growth. In dementia, the cranial nerve is destroyed by various causes causing disorders in general in mental functions, such as memory disorder, language disorder, urinary / fecal incontinence, paranoia and aphasia. Moreover, the progress of dementia may be accompanied by psychological symptoms such as melancholy, personality disorder and aggression. In the medical field, aging and inheritance have been highlighted as the causes of dementia. However, an exact cause of the disease and method of treatment has not yet been discovered. Diseases classified as dementia include, but are not limited to, Alzheimer's dementia, cerebrovascular dementia, senile dementia, and brain injury dementia.

The composition for use according to the present invention comprises toosendanin or a pharmaceutically acceptable salt thereof as an active ingredient that any extract may comprise provided that the extract comprises toosendanine as an active ingredient. For example, the extract may be a Cedrela sinensis extract or cinnamon extract, although the present invention is not limited thereto. Preferably, it can be a cinnamon extract (Melia azedarach or Melia toosendan), and more preferably it can be an extract from toosendan fructus (cinnamon fruit) or Meliae cortex (candle or cinnamon bark).

The two cinnamon species (Melia azedarach and Melia toosendan) are classified in the Meliaceae family and in the Melia genus. Its canopy or bark (called Meliae cortex) and its fruit (Toosendan Fructus) have been used mainly as anthelmintics since ancient times (in China), also show antibacterial, diuretic and antipyretic effects. Also, according to the annotations in Donguibogam, they can be used for the treatment of scrotal hernia (inflammation or pain in the reproductive system / testicles, and urinary and fecal disorder). The cinnamon extract (Melia azedarach or Melia toosendan) of the present invention can be extracted and prepared from any part of the cinnamon, such as fruits, leaves, stems, roots, and preferably can be prepared from fruits, barks of stem or stem bark.

The cinnamon extract used (Melia azedarach or Melia toosendan) of the present invention can be prepared by an extraction method known in the art. As the extraction solvent, for example, any solvent selected from water, from the group that includes organic solvents such as C1 to C6 alcohol such as ethanol (ethyl alcohol), methanol, ethyl acetate, dichloromethane, chloroform, n-hexane, can be used. diethyl ether, acetone, benzene, or a mixed solvent thereof. Preferably, C1 to C6 water or alcohol can be used for extraction. When the solvent extraction method is used for the preparation of an extract, hot water extraction, ultrasonic extraction, and reflux extraction can be used. More preferably, the cinnamon extract used in the present invention can be extracted or prepared using methanol as a solvent. The proportion of cinnamon and methanol in the extraction is not particularly limited, although methanol can be added to the cinnamon in an amount of 3 ~ 15 times with respect to the cinnamon's weight. Preferably, to increase the extraction efficiency, methanol can be added to the cinnamon in an amount of 5 ~ 10 times relative to the weight of the cinnamon. The extraction temperature may preferably range between 10-30 ° C under atmospheric pressure. Also, the extraction time may vary according to the extraction temperature, but may range between 48-96 hours, and preferably may be 72 hours. When the extraction time is short, the extraction of a cinnamon component is insufficient. On the other hand, when the extraction time is too long, the extraction performance is reduced by evaporation. Also, in order to increase the extraction efficiency, preferably, the cinnamon can be ground by a mill, and the methanol extraction step can be repeated twice to further extract a residual component.

The extract extracted by methanol can be fractionated by a method known in the art to remove impurities and increase the concentration of an active ingredient. In order to increase the efficiency of fractionation, the extract can be concentrated in vacuo. As the solvent for fractionation, any one of the group including solvents such as C1 to C6 alcohol, such as ethanol and methanol, ethyl acetate, dichloromethane, chloroform, n-hexane, diethyl ether, acetone, benzene, or a solvent can be used. mixed them. Preferably, ethyl acetate can be used for fractionation. A fraction can be used as it is, or it can be split again. In refraction, preferably, a solvent mixed with water, methanol and n-hexane can be used. 55

In an example of the present invention, toosendan fructus ground into small pieces was extracted twice in methanol in a volume 5 times greater than the weight of toosendan fructus for 3 days, and an extract was filtered, concentrated in vacuo, suspended in water, and treated with ethyl acetate in the same volume. Then, a fraction of ethyl acetate was collected and concentrated in vacuo. The concentrated fraction was added with methanol and 90 ~ 95% n-hexane in the same volume, then stirred. Later, a

fraction of methanol was collected, concentrated in vacuo, and a final extract was obtained (See Example 1).

The toosendanine used in the present invention can be separated / purified from natural material, commercially available, or prepared by a chemical synthesis method known in the art. 65

Preferably, the toosendanine used in the present invention can be separated / purified from a natural material. More preferably, it can be separated / purified from Melia toosendan, and even more preferably, it can be separated / purified from toosendan fructus (cinnamon fruit) or Meliae cortex (bark of a root or stem of Melia toosendan). One method of obtaining an extract containing Melosen toosendanin from Melia toosendan is the same as described above. The separation of toosendanine from the extract can be carried out according to the method of chromatographic separation known in the art. For example, during fractionation using silica column chromatography, and high efficiency liquid chromatography (HPLC), an active ingredient can be purified.

In an example of the present invention, cinnamon extract (Melia azedarach or Melia toosendan) was divided into 8 parts by silica mesh 60 while gradually increasing the proportion of the mixture (100% dichloromethane) : 0% methanol to 0% dichloromethane: 100% methanol). The fractions were then obtained. Then, a part with the highest activity (dichloromethane: methanol = 25: 1) was fractionated through the octadecylsilylated silica resin while the methanol concentration was varied. A fraction with the highest activity was then secured, and again fractionated under the same conditions by changing the methanol concentration. A fraction with the highest activity was ensured, and during HPLC fractionation, toosendanin was purified (See Example 2). The final fraction was identified as toosendanin through an NMR spectroscopy analysis and mass spectrometry.

Toosendanine as an active ingredient in the composition for use according to the present invention or cinnamon extract (Melia azedarach or Melia toosendan) inhibits the activity of β-secretase, and promotes the activity of α-secretase. Finally, it has an inhibitory activity of beta amyloid production. This was first discovered by the inventors of the present invention.

Alzheimer's disease is mainly caused by Aβ and a Tau protein, forming a senile plaque and an external and internal nerve fiber, respectively, of neurons. This causes atrophy of a brain tissue, and memory disorder. Between Aβ and Tau, Aβ is closely related to the direct death of a neuron. In Alzheimer's disease, activation in the PPA production pathway to Aβ is assumed to induce an initial symptom due to some reason, and a Tau protein is related to the acceleration of the disease (Small and Duff, Neuron, 2008 , 5: 591-598). Consequently, it is believed that for the prevention or treatment of Alzheimer's disease, in the first place, blockage of the Aβ production pathway is important. PPA is cleaved into the C-terminal β fragment (CTFβ) that includes an amino acid sequence of PPAβ and Aβ by β-secretase, and then formed during the action of γ-secretase in CTFβ, AICD (intracellular domain of the PPA), and Aβ. Thus, inhibition of β-secretase activity can be a method for the prevention or treatment of Alzheimer's disease. Likewise, α-secretase decomposes PPA competitively with respect to β-secretase, thereby inhibiting the production of Aβ. Using α-secretase, the production of PPAα (one of the metabolites of PPA) is induced. Thus, improving the activity of α-secretase may be another method to prevent or treat Alzheimer's disease.

The composition for use according to the present invention or toosendanin as an active ingredient in the composition for use according to the present invention is an inhibitor of Aβ production that effectively blocks the Aβ production pathway, and favors the production of PPAα which shows a protective effect of the neuron, corresponding to the object described above on the development of an agent for the treatment of Alzheimer's disease.

Four. Five

In an Example of the present invention, it was discovered that during a Western Blot cell experiment, cinnamon or toosendanine extract in the composition for use according to the present invention favors the production of PPAα, and inhibits the production of PPAβ (see Example 5-1), and also, it was discovered that during the cell experiment by a quantitative beta amyloid analysis kit, these inhibited the production of beta amyloid (see Example 5-2). fifty

In an Example of the present invention, it was discovered that during an animal experiment by a quantitative beta amyloid analysis kit, cinnamon or toosendanine extract in the composition for use according to the present invention reduces the level of beta amyloid in an animal model of dementia (See Example 8).

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In an Example of the present invention, it was discovered that cinnamon or toosendanine extract in the composition for use according to the present invention, treats cognitive memory / dysfunction (one of the main symptoms of dementia) in an animal model of dementia during a Y labyrinth test, a water maze test, and a passive avoidance test in a dementia-induced rat that is administered with the composition for use according to the present invention (See Example 7). 60

Accordingly, it was determined that the composition for use according to the present invention shows a significant effect on the prevention or treatment of dementia while effectively blocking an Aβ production pathway and promoting the production of PPAα showing a protective effect. of a neuron

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In another Example of the present invention, using ethyl alcohol (ethanol) with various concentrations as an extraction solvent, cinnamon extract in the composition for use according to the present invention was obtained, and the toxicity and efficacy of the respective extracts were compared. each. As a result, when the cinnamon extract used in the present invention was extracted by ethyl alcohol as the extraction solvent, it generally shows high efficacy regardless of the concentration of ethyl alcohol. In particular, when the ethyl alcohol content of an extraction solvent was adjusted from 30% to 50%, it was determined that it is possible to secure the cinnamon extract used of the present invention with high efficiency and very low toxicity (See Example 9).

Thus, the present invention presents a pharmaceutical composition for use in the prevention or treatment of dementia, comprising toosendanine or a pharmaceutically acceptable salt thereof as an active ingredient. Furthermore, the present invention presents a pharmaceutical composition for use in the prevention or treatment of dementia, comprising cinnamon extract (Melia azedarach or Melia toosendan) as an active ingredient. A pharmaceutical composition for use according to the present

invention may comprise between 0.001 to 99.999% by weight of the cinnamon extract (Melia azadarach or Melia 15 toosendan) or toosendanine or a pharmaceutically acceptable salt thereof and the rest may be a pharmaceutically acceptable carrier.

The toosendanine used in the present invention can be used alone or in the form of a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable" refers to the components present in the composition being physiologically acceptable and generally do not cause allergic or similar reactions when administered to humans. Preferably, the salt may be an acid addition salt formed from a pharmaceutically acceptable free acid. The free acid can be an organic or inorganic acid. Organic acid includes but is not limited to citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, benzoic acid, gluconic acid, methanesulfonic acid, acid glycolic, succinic acid, 4-toluenesulfonic acid, glutamic acid and aspartic acid. Inorganic acid includes but is not limited to hydrochloric acid, bromic acid, sulfuric acid and phosphoric acid.

A pharmaceutical composition for use according to the present invention may comprise toosendanin or a pharmaceutically acceptable salt thereof or cinnamon single extract (Melia azedarach or Melia toosendan) or further comprise pharmaceutically acceptable carriers, excipients or diluents.

As used herein, the term "pharmaceutically acceptable" refers to the components present in the composition not having a physiologically acceptable toxic composition and in general does not cause allergic reactions such as gastrointestinal disorders, dizziness or similar reactions when Manage humans.

A pharmaceutically acceptable carrier can be understood, for example, carriers for parenteral or oral preparations. The carriers for oral preparations may comprise lactose, starch, cellulose derivatives, magnesium stearate, and stearic acid. In addition, they may comprise various drug distribution materials for administration of peptide agents. The carriers for parenteral preparations may comprise water, appropriate oil, saline, aqueous glucose and glycol. They can also comprise stabilizers and preservatives. Examples of stabilizers may be antioxidants such as sodium hydrogen sulfite, sodium sulfite, and ascorbic acid. Examples of preservatives can be benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. A pharmaceutical composition for use according to the present invention may further comprise lubricants, wetting agents, sweetening agents, seasonings, emulsifying agents and suspending agents. The list of pharmaceutically acceptable carriers is described in Remington Sciences Pharmaceutical, 19th ed., Mack Publishing Company, Easton, PA, 1995. 50

A pharmaceutical composition for use according to the present invention comprising cinnamon extract (Melia azedarach or Melia toosendan), toosendanine or a pharmaceutically acceptable salt thereof as an active ingredient, may comprise an effective amount of cinnamon extract (Melia azedarach or Melia toosendan), toosendanin or only pharmaceutically acceptable salt thereof or further comprise pharmaceutically acceptable carriers. As used herein, "pharmaceutically acceptable amount" refers to the amount that shows more reaction than the negative control and preferably refers to the amount sufficient to treat or prevent dementia. As used herein, dementia can be Alzheimer's disease, cerebrovascular dementia, senile dementia and dementia caused by a brain injury.

A composition for use according to the present invention can be administered to mammals as well as to 60 humans by various routes. For example, it can be administered orally or parenterally. For parenteral administration, it can be administered by, but not limited to, intravenous, intramuscular, intraarterial,

intraosseous, subdural, intracardiac, intracutaneous, subcutaneous, intraperitoneal, intranasal, gastrointestinal, parenteral, sublingual or rectal.

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A pharmaceutical composition for use according to the present invention can be prepared in a formulation for oral administration or parenteral administration, as described above.

In the case of the formulation for oral administration, the composition for use according to the present invention may be formulated in powders, granules, tablets, pills, and sugar-coated tablets, 5 capsules, liquids, gels, syrups, suspensions, and emulsions using The method known in the art. For example, sugar-coated tablets or tablets may be prepared by mixing an active ingredient with a solid excipient, grinding, and then adding an appropriate adjuvant. Examples of suitable excipients may comprise sugars comprising lactose, dextrose, sucrose, sorbitol, mannitol, xylitol, erythritol and maltitol, starches comprising corn starch, wheat starch, rice starch and potato starch, cellulose comprising cellulose , methylcellulose, sodium carboxymethylcellulose and hydroxypropylmethylcellulose, and fillers comprising gelatin and polyvinylpyrrolidone. If desired, it can comprise as crosslinked polyvinylpyrrolidone thickener, agar, alginic acid or sodium alginate. In addition, the pharmaceutical composition for use according to the present invention may comprise an anticoagulant agent, a lubricant, wetting agents, seasonings, emulsifying and antiseptic agents. fifteen

In the case of parenteral preparations, these include injections, creams, lotions, ointments, oils, humectants, gels, and aerosols. The formulation of those mentioned above is well described in Remington Science Pharmaceutical, 15th edition, 1975.

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The total effective amount of pharmaceutical composition for use according to the present invention can be administered to a subject as a single dose, or it can be administered using a fractional treatment protocol, in which multiple doses are administered over a longer period. The pharmaceutical composition for use according to the present invention may vary in the amount of the effective component depending on the severity and / or object of the disease, but preferably, it may be administered between 0.01 µg 25 / kg to 500 mg / kg, and more preferably 0.1 µg / kg at 100 mg / kg per day. However, one skilled in the art would know that the concentration of toosendanin or cinnamon extract (Melia azedarach or Melia toosendan) to obtain an effective dose in a subject depends on various factors including age, body weight, health status, the severity of the disease, the diet and excretion of the subject, the route of administration, the number of treatments to be administered, etc. In view of these factors, any person skilled in the art can determine the appropriate effective dose of toosendanine or cinnamon extract (Melia azedarach or Melia toosendan) to prevent or inhibit dementia. No particular limitation is imposed on the formulation, route of administration and mode of administration of the pharmaceutical composition for use according to the present invention, as long as the composition shows the effects of the present invention.

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The present invention presents a use of toosendanin or pharmaceutically acceptable salt thereof for the preparation of an agent to prevent or treat dementia.

The present invention presents a use of cinnamon extract (Melia azedarach or Melia toosendan) for the preparation of an agent to prevent or treat dementia. 40

For the prevention or treatment of dementia, an effective amount of toosendanine or pharmaceutically acceptable salt thereof is administered to a subject in need thereof.

For the prevention or treatment of dementia, an effective amount of cinnamon extract (Melia azedarach or Melia toosendan) is administered to a subject in need.

The toosendanine or pharmaceutically acceptable salt thereof, the cinnamon extract (Melia azedarach or Melia toosendan) used in the present invention can be administered with an effective amount by various routes including the oral, intracutaneous, subcutaneous, intravenous, or intramuscular route. As used herein, the "effective amount" refers to the amount effective in the treatment of dementia when administered to a patient.

As used herein, the "subject" refers to mammals, in particular, animals including humans and may be a cell, tissue or organ originating from the animal. The subject may be a patient who needs treatment.

The toosendanine or pharmaceutically acceptable salt thereof, the cinnamon extract (Melia azedarach or Melia toosendan) used in the present invention can be administered alone or by various formulations mentioned above, and preferably can be administered until the effect is deduced. in dementia

Advantageous effects

Thus, the pharmaceutical composition for use according to the present invention which includes cinnamon extract, toosendanin, or its pharmaceutically acceptable salt, as active ingredient, is very effective.

in the prevention or treatment of dementia. In particular, the composition, for use according to the present invention, is effective in inhibiting the production of Aβ and in inducing the improvement of PPAα production that shows a protective effect of a neuron. Therefore, it is very effective in the prevention or treatment of dementia such as Alzheimer's disease. Thus, the pharmaceutical composition for use according to the present invention that includes cinnamon extract, or toosendanine, as an active ingredient, can be used in several areas such as the preparation of preventive / treatment drugs for patients with dementia or persons of susceptible age. dementia.

Description of the drawings

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Figure 1 is a diagram showing a process for obtaining toosendanine according to the present invention, an extract of toosendan fructus and a fraction including toosendanine;

Figure 2 shows the result of the measurement of the effect on the production of PPAα and PPAβ (metabolites of PPA) by toosendanin, and extracts of toosendan fructus from the respective organic solvent that includes toosendanin, in which the measurement was carried out by Western Blot (control,

c: a control group not treated with an extract; MeOH: a group treated with a methanol extract from toosendan fructus);

Figure 3 shows the result of measuring the effect on the production of PPAβ (PPA metabolites) by meliae cortex extracts, in which the measurement was carried out by Western Blot (EtOH: a group treated with ethanol extract of meliae cortex; MeOH: a group treated with meliae cortex methanol extract; AE: a group treated with a meliae cortex ethyl acetate extract; hexane: a group treated with 20 meliae cortex n-hexane extract; and C : a control group not treated with any extract);

Figure 4 shows a graph of a result of the measurement of the amount of Aβ40 when a CHO cell line overexpresses BACE1 and the Swedish mutation of PPA695 was treated with toosendan fructus ethyl alcohol extract, in which the measurement was carried out by an Aβ40 quantitative analysis kit to determine if the production of Aβ40 was inhibited; 25

Figure 5 shows a graph of a comparative measurement of spontaneous alternation behavior (%) in a Y labyrinth test of a rat with dementia, in which the measurement was carried out to determine the effect of ethyl alcohol extract from toosendan fructus in memory improvement (% of alternation: alternating behavior (%); vehicle: a control group administered with only 10% of Labrasol without any extract; and toosendan fructus: a group administered with ethyl alcohol extract of 30 toosendan fructus);

Figure 6 shows a graph of a result of a comparative measurement of the time required to find a platform in the water labyrinth test of a rat with dementia, in which the measurement was carried out to determine the effect of the alcohol extract ethyl alcohol of toosendan fructus in memory improvement (Escape latency time (s): time needed to find a platform (s); vehicle: a control group 35 administered with only 10% of Labrasol without extract some; and toosendan fructus: a group administered with ethyl alcohol extract of toosendan fructus);

Figure 7 shows a graph of the result of the measurement of the time required to enter a dark room in a passive avoidance test of a rat with dementia, in which the measurement was carried out to determine the effect of ethyl alcohol extract of toosendan fructus in memory improvement 40 (Escape latency time (s): time needed to enter a dark room (s); vehicle: a managed control group with only 10% of Labrasol without any extract; and toosendan fructus: a group administered with extract of ethyl alcohol from toosendan fructus);

Figure 8 shows a graph of the result of the measurement of the amount of Aβ40 in a brain tissue of a rat, in which the measurement was carried out by a quantitative analysis kit Aβ40 to determine if the production of the extract was inhibited. of ethyl alcohol of toosendan fructus in the brain tissue of a rat with dementia;

Figure 9 shows a graph of the result of the measurement of the amount of Aβ40 in a rat serum in which the measurement was carried out by a quantitative analysis kit Aβ40 to determine if the production of Aβ40 was inhibited in the blood of the rat administered with toosendanine (Vehicle: a control group administered with only 20% ethyl alcohol without toosendanine; and 5 mg / kg, 50 mg / kg: experimental groups administered with 50 toosendanine at a dose of 5 mg / kg, and 50 mg / kg, respectively;

Figure 10 shows a photograph of a comparative result of the changes in the effectiveness of the composition for the inhibition of PPAβ production or to favor the production of PPAα, according to extraction solvents, in which the result was measured by Western Blot (100% ethyl alcohol to 30% ethyl alcohol: a group administered with cinnamon extract extracted by a solvent mixed with water and ethyl alcohol of respective proportions (%); and C: a control group not treated with extracts); Y

Figure 11 shows a graph of a result of the measurement of the changes in the efficacy of the composition for the inhibition of Aβ production, according to the extraction solvents (100% ethyl alcohol to 50% ethyl alcohol: a group administered with Cinnamon extract extracted by a solvent mixed with water and ethyl alcohol of respective proportions (%)). 60

Mode of the invention

Next, the present invention will be described in detail with reference to the Examples.

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However, the following Examples illustrate the invention and are not intended to limit it.

<Example 1>

Extraction and fractionation of toosendan fructus and meliae cortex

Toosendan finely ground fructus (dry weight: 10 kg) was immersed in 50 L of methanol for 3-5 days for extraction. This step was repeated twice. The extract was then collected, filtered and concentrated in vacuo. The concentrate obtained was added to 10 L of water, suspended and added to the same volume of ethyl acetate, mixed and allowed to stand. Then, a solvent fraction of ethyl acetate was collected and concentrated in vacuo. For other fractions of the ethyl acetate concentrate, 10 L of 90 ~ 95% methanol (5 ~ 10% water) and 10 L of n-hexane were added thereto, and then mixed and allowed to stand. Then, a 90 ~ 95% methanol fraction was collected and concentrated in vacuo. The respective fractions obtained in the extraction and fractionation stages were used for the activity analysis and kept at 4 ° C until their active ingredients were separated. Meliae cortex was also extracted by the same method and the same respective solvent extracts were obtained.

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<Example 2>

Separation of an active subfraction ingredient from toosendan fructus

From the concentrate of the 90 ~ 95% methanol fraction obtained in Example 1, an active ingredient 20 was separated. The concentrate was divided into 8 sub-fractions of silica resin (60 mesh), while the proportion of methanol mixture gradually increased (from 100% dichloromethane: 0% methanol to 0% dichloromethane: 100% methanol). Of these, 3 fractions with activity (dichloromethane: Methanol = 25: 1, 10: 1 5: 1) were obtained. The 25: 1 fraction concentrate with the highest activity was fractionated through octadecylsilylated silica resin (Biotage FLASH + ™, C18HS 25 + M, 60Å, 40-63 μm, FPK0 - 1107 - 16046, 10 ml / min) while the concentration of MeOH was increased from 15% to 100% in stages. After examining the activities, an active fraction of 35% to 50% was obtained. This active fraction was

refracted under the same conditions by changing the concentration (30 ~ 100%) of MeOH. Next, an active fraction (40 ~ 60%) was obtained and concentrated. From the concentrate, an active ingredient was purified by using a mixed solvent of acetonitrile and water as the separation solvent (48% acetonitrile), through high performance liquid chromatography (HPLC) using an octadecylsilylated silica resin (Pack YMC ODS - A, 150 × 10 mm id, 120Å, S - 5 μm, AA12S05 - 1510WT) at a flow rate of 4 ml / min (see Figure 1).

The purified active ingredient was identified as toosendanin, represented by Formula 1 through structural analysis and molecular weight determination through the use of an NMR 35 spectroscopy analysis and mass spectrometry.

<Example 3>

Measurement of the content of toosendanin in an ethyl alcohol extract of fructus toosendan 40

In order to carry out an efficacy test of an ethyl alcohol extract, the content of toosendanin (as an indicator / active ingredient) in the ethyl alcohol extract was measured. Toosendanine was analyzed using 30% acetonitrile containing 0.05% TFA (trifluoroacetic acid) as elution solvent, by HPLC using octadecylsilylated silica resin (Pack YMC ODS-A, 150 × 10 mm Id, S-5 μm) as a column, at a flow rate of 1 ml / min at 214 nm. The purchased toosendanin reference material was diluted to an appropriate concentration, and the area value was measured according to a concentration. Based on this, an absolute calibration curve of the area-concentration ratio was performed on a chromatogram of the reference material and the linearity was determined to be 0.999. Next, the curve was used for quantification. Toosendanine exists naturally in the form of isomers and, therefore, was detected (after 15.7 minutes and 20.6 50 minutes, respectively) in the analysis condition described above. For more exact quantification, an ethanol extract of toosendan fructus was suspended in distilled water, fractionated in solvent by ethyl acetate, and concentrated. The concentrate was used for the analysis. When the quantitative analysis by substitution in the calibration curve was carried out, it was found that toosendanine was in an amount of approximately 1.15% of the extract of ethyl alcohol from toosendan fructus. 55

<Example 4>

Cytotoxicity measurement of an extract of ethyl alcohol from toosendan fructus

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Cytotoxicity was measured by an MTT method. As cell lines, the BA-3 cell line derived from HEK293 (Yeon et. Al., Peptides, 2007, 28: 838-844) was used to be used for a production inhibition test PPAβ, HL60 (cell line human leukemia), and HepG2 (human liver cancer cell line). The cells were seeded in a 96-well plate at a concentration of 1 × 104/90 ul / well, and cultured for 1 day. Each material dissolved in DMSO was diluted by a culture medium so that a final concentration can be 1%, and then each cell line was treated with the material, and cultured

for 3 days. After cultivation, the state of the cells was observed by a microscope. An MTT solution [3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyl-2H tetrazolium bromide, 5 mg / ml in PBS] was added in an amount of 15 ul to each well, followed by a reaction for 4 hours at 37 ° C. Each well was treated with

100 ul of lysis buffer (0.01 N HCl, 10% SDS), and left at 37 ° C for 24 hours so that the formazan formed could dissolve completely. Next, the absorbance at 570/652 nm was measured. As a result, BA-3 treated with toosendan fructus ethyl alcohol extract showed no cytotoxicity even at the highest concentration of 100 ug / ml, while toosendan fructus ethyl alcohol extract showed a slightly growth-inhibiting effect. mobile. Through microscopic observation, cytotoxicity was not found in HepG2 and HL60, treated with the extract of ethyl alcohol from toosendan fructus, while cell growth was inhibited. When toosendan Fructus extract inhibited cell growth by 50%, its concentrations were 3.2 ug / 10 ml and 34 ug / ml, respectively.

<Example 5>

Analysis of a metabolic inhibitory effect of an amyloid precursor protein (PPA) by an extract of toosendan Fructus and toosendanin in a cell

<5 - 1> PPAβ production inhibitory effect

A BA-3 cell line derived from HEK293 that overexpresses 20 BACE1 (β-secretase) and PPA695 was placed in a 6-well plate using DMEM (Dulbecco's Modified Eagle Medium) that includes 10% bovine fetal serum (SFB) in such a way that it occupied 80% or more of the area of each well, and then it was cultivated for 1 day. After removal of the culture medium, the free DMEM (not including bovine fetal serum) was heated to 37 ° C, and added in an amount of 0.9 ml to each well. Next, toosendanin or a fraction of toosendan fructus was extracted with each solvent diluted to an appropriate concentration by free DMEM of 0.1 ml, and the cell line was treated with these materials, and cultured for 24 hours. 0.2 ml of the culture medium treated with each test sample was collected and electrophoresed in 8% SDS-PAGE (polyacrylamide gel electrophoresis). Next, the AB1560 (monoclonal) and Rb53 (polyclonal) antibodies (antibodies against PPAα and PPAβ) were used to measure the amounts of PPAα and PPAβ from the culture medium through Western Blot. 30

As a result, it was found that extracts of methanol / ethyl alcohol / alcohol / ethyl alcohol from toosendan fructus inhibited the production of PPAβ, and favored the production of PPAα. In a test on the effect of the inhibitory production of PPAβ and the favorable production of PPAα according to dilution concentrations of the ethyl alcohol extract, when the treatment concentration of the extract was 6.25 ug / ml, the production of PPAβ it was reduced to 27.7%, and the production of PPAα was increased to 131.3%, with respect to an untreated group (control, 100%). On the other hand, even when the treatment concentration of the extract was lower (less than 0.05 μg / ml), an inhibition effect dependent on the concentration of PPAβ was achieved and the production of PPAα was favored. It was also found that purified toosendanin, even at a concentration of 12.5 nM or less, inhibited the production of PPAβ while favoring the production of PPAα (at 0.8 um, the production of PPAβ reduced to 17.8%, and the production of PPAα increased to 141.5%, compared to an untreated group). Therefore, it can be determined that these materials strongly inhibit the PPA inhibitory metabolism that favors the production of Aβ (see Figure 2).

Extracts (ethyl alcohol, methanol, ethyl acetate, and 90% methanol) were obtained from meliae cortex 45 (cinnamon bark) under the same organic solvent extraction condition as toosedan Fructus. Next, its effects on reducing the production of PPAβ were tested. As a result, each extract showed a reducing

effect of PPAβ production at 12.5 - 6.25 μg / ml although the effect was less than that of toosendan Fructus extract (see Figure 3.).

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<5 - 2> Inhibitory effect of Aß production by an extract of toosendan fructus

The BACE1 genes (GenBank access number; AF190725) and the Swedish mutation of PPA695 (GenBank access number; MIM: 104760,008) were introduced into pcDNA3.1 / Myc-His (Invitrogen, USA) and pcDNA3.1 vectors / Hygro (Invitrogen, USA), respectively, and were introduced into CHO cell lines. Then, using a cell line that overexpresses BACE1 proteins and Swedish mutation PPA695, it was tested if the extract toosendan fructus inhibited the production of Aβ40. CHO cell lines were cultured in a 6-well plate using DMEM with 10% SFB (fetal bovine serum) such that it was included in an appropriate amount in each well, and cultured for 1 day. After removal of the culture medium, the free DMEM (which did not include fetal bovine serum) was heated to 37 ° C, and added in an amount of 0.9 ml to each well. Next, an extract of toosendan Fructus was diluted with toosendanine to an appropriate concentration by 0.1 ml of free DMEM, the cell lines were treated with the extract, and cultured for 24 hours. Next, the culture medium was separated, and the quantitative analysis was carried out by means of the quantitative analysis kit Aß40 (High Specific Assay Kit Amyloidβ (1-40), BioSource, CA) from BioSource (CA, USA).).

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As a result, it was observed that the extract of ethyl alcohol from toosendan fructus (10 ug / ml or less) showed an inhibitory effect of Aβ40 production of 50% or more (see Figure 4).

<Example 6>

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Toxicity test on an extract of ethyl alcohol from toosendan fructus

In order to determine whether oral administration of the alcohol extract of toosendan fructus with toosendanine causes toxicity, toxicity tests of a single dose and 4 weeks of multiple doses were carried out. 10

In the single dose toxicity test, each group, which included 5 male ICR rats (6 weeks), was given orally an extract of ethyl alcohol from toosendan fructus in a single dose in an amount of 750 ~ 3000 mg / kg It was observed for 2 weeks if the experimental animals survived, and then through euthanasia and autopsy, abnormal organ findings were observed. It was found that administration of the extract in an amount of 1,500 mg / kg or more caused toxicity, as some of the rats died. On the other hand, it was discovered that administration of the extract in an amount of 1,000 mg / kg or less did not cause toxicity, since no rat died and no abnormal organ findings were observed.

In the multiple dose toxicity test, each group, which included 6 male ICR rats (6 weeks), 20 was given orally an extract of ethyl alcohol from toosendan fructus in an amount of 125 ~ 1,000 mg / kg once a day for 26 days. A change in weight, general symptoms, and mortality of the experimental animals was observed, and through euthanasia and autopsy, abnormal findings were observed in the organs. As a

result of the test, it was found that a maximum tolerance dose (BAT) was 750 ~ 1000 mg / kg, and a level without observable adverse effect (NOAEL) was 500 mg / kg. 25

<Example 7>

An effect on the improvement of memory and cognitive function by an extract of ethyl alcohol from toosendan fructus in an animal model of dementia 30

An extract of ethyl alcohol from toosendan fructus in suspension in 10% Labrasol was administered orally to 6 rats with dementia (transformed to produce the Swedish PPA mutation) in an amount of 300 mg / kg (5 times per week) for 3 months. Next, a Y-maze test, a water maze test, and a passive avoidance test were carried out, and it was analyzed whether a memory improvement was achieved unlike a group of vehicles (which were administered with 10% labrasol, 5 rats).

<7 - 1> Y labyrinth test

The test was carried out using a Y-labyrinth measuring device with 3 arms (each arm: 25 40 (L) x 14 (A) x 5 (A) (cm)) form a letter Y (arm) at angles uniforms First, the head of an experimental animal was directed toward one end of the arm of labyrinth Y, and the animal was allowed to run freely around the arms for 8 minutes. When the hind leg of the rat with dementia entered the arm it was recognized as an entry in the arm. The movement was recorded as alternation. Next, 3 sequential entries were recognized as real alternation, and they were given 1 point. Next, the behavior of spontaneous alternation (%) was obtained by means of the percentage of the real alternation and the possible maximum alternation (= total alternation - 2).

As a result, the group to which the alcohol extract of toosendan fructus with toosendanine was administered showed a spontaneous alternation behavior of 62.6 ± 3.1%, and the vehicle group (10% 50 of Labrasol) showed 53, 9 ± 3.4%. Therefore, it was found that administration of toosendan fructus ethyl alcohol extract showed an improvement in memory of 16.1% with a reliability of 95% or more ($p < 0.05$) (see Figure 5).

<7 - 2> Water maze test 55

A reference memory test was carried out for the water maze test after allowing the rats to swim freely and adapt in a platformless water tank for 60 seconds, one day before starting the test. In the test, the time (escape latency, unit: seconds) required to find and mount to the platform submerged in water was measured 4 to 5 times per day, for 5 days, and the maximum tolerance time 60 was limited to 60 seconds. Until the second day of the test, when a rat could not find the position of the platform, it was guided to discover it in 60 seconds (time limit). Then, once he had mounted the platform, he was allowed to remain there for 10 seconds.

After 24 hours from the end of the reference memory test, the platform inside the water tank was removed, and the rats were allowed to swim freely for 60 seconds. Then it was done

a trial of the test while measuring the time of permanence of a rat in the position (where the platform was the previous days).

As a result, in the reference memory test, a vehicle group showed no improvement in the time required to find the platform during the test period, while a group that was administered an extract of ethyl alcohol from toosendan fructus discovered the platform in a shorter time than the vehicle group, from the second day of the test. Then, from the fourth day of the test, the difference between the group to which the extract was administered and the vehicle group was maximized (see Figure 6). In the test trial, the group to which the extract was administered showed a 33.0 ± 3.2% permanence rate in the position (where the platform was in the previous days), while the vehicle group showed a proportion of 14.0 ± 5.8%. It was found that the group to which the extract was administered remained 2.35 times or more ($p < 0.05$) with statistical significance.

<7 - 3> Passive Avoidance Test

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The passive avoidance test was carried out using a shuttle-box with 2 compartments separated by a sash door. One compartment lit up, while the other darkened, covering it with a black cloth and no lighting. On the first day, a rat with dementia stayed in the lighted room with a search time of 30 seconds, and then the guillotine door was opened so that the rat could enter the dark room. Next, the latency acquisition time required to enter the darkroom was measured. Once the rat entered the dark room, the guillotine door was closed, and an electric shock of 0.5 mA was applied to the rat for 3 seconds through a half-timbered floor, so that it can remember the electric shock. After 24 hours, the rat with dementia was left in the bright room, with a search time of 30 seconds and then the guillotine door opened. Next, a retention latency time required to enter the dark room (all rat legs (maximum of 300 seconds) was measured. It was determined that as the latency retention time increases, the memory in passive avoidance through learning.

When the latency retention time required to enter the dark room was measured after learning an electric shock, a group to which an extract of ethyl alcohol from toosendan 30 fructus was administered showed a latency retention time of 288.8 ± 9.2 seconds, and a vehicle group showed a latency retention time of 131.8 ± 59.6 seconds. In other words, it was found that the group to which the extract was administered showed an improvement in passive avoidance memory of 220% or more, with a reliability of 95% or more (see Figure 7). Consequently, it was found that the composition for use according to the present invention has a significant effect in the treatment of memory / cognition dysfunction caused by dementia.

<Example 8>

Aβ inhibitory effect by ethyl alcohol extract of toosendan fructus and toosendanine in 40 living body

<8 - 1> Aβ inhibitory effect by ethyl alcohol extract of toosendan fructus in a rat with transformed dementia

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After finishing the memory test, a transformed rat brain was removed. Then, in a brain tissue, the change of Aß was measured. The extracted brain was weighed, and added to a cooled solution A (5 M guanidine HCl, 50 mM Tris HCl) in a volume 8 times greater than the weight. Next, the brain tissue was

ground and homogenized by a homogenizer, and left at room temperature for 3 ~ 4 hours, followed by centrifugation (16,000 xg, 20 minutes, 4 ° C). A supernatant was collected to remove brain tissue. The collected supernatant was diluted 3,200 times in a solution B (phosphate buffered saline, 5% BSA, 0.03% Tween-20, pH 7.4, protease inhibitor cocktail), and A40 was quantified by the use of an Aß40 quantitative analysis kit from BioSource (CA, USA).

As a result, when the value of Aß40 was measured with respect to the weight of brain tissue diluted 3,200 times, the value of a vehicle group was 362.5 ± 20.7 pg / ml, and the value of a group to which the Toosendan fructus ethyl alcohol extract was 111.9 ± 84.6 pg / ml. In other words, administration of toosendan fructus ethyl alcohol extract reduced Aβ40 by approximately 69% (see Figure 8).

<8 - 2> Inhibitory effect of Aβ by toosendanin in a rat

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Blood was drawn before the administration of toosendanine. Toosendanin was then administered in suspension in 20% ethyl alcohol orally in doses of 5 and 50 mg / kg. After two hours, blood was collected, and the change in Aβ concentration in blood was measured before / after administration. The collected blood was centrifuged (16,000 xg, 20 minutes, 4 ° C), and the A40 collected in the serum was quantified using a quantitative analysis kit Aß40 (High Specific Assay Kit Amyloidβ mouse / rat (1-40), IBL , Japan). 65

As a result, a vehicle group showed an increase of Aß40 by about 40% with the administration, without statistical significance. In addition, it was found that administration of toosendanin (5 mg / kg) inhibited Aβ40 by 85% or more. From this result, it is expected that if toosendanine is administered at a lower dose, the production of Aß40 can be inhibited (see Figure 9). Accordingly, it was determined that the composition for use according to the present invention is highly effective in the prevention or treatment of dementia by inhibiting the production of Aβ.

<Example 9>

Toxicity and efficacy test according to an extraction solvent 10

In order to obtain an extract of lower toxicity capable of maintaining the effectiveness of the composition for use according to the present invention, toosendan Fructus was extracted by varying the content of ethyl alcohol in an extraction solvent, and toxicity tests were carried out and of efficiency.

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<9 - 1> Preparation of an extract of ethyl alcohol from toosendan fructus

10 kg of ground toosendan fructus was immersed in 50 L of ethyl alcohol (100%, 70%, 50% and 30%) for 3 days for extraction. Then, the extract was filtered, concentrated in vacuo, and lyophilized to obtain an extract of ethyl alcohol from toosendan fructus. twenty

<9 - 2> Repetitive toxicity test on an extract of ethyl alcohol from toosendan fructus

A vehicle group and three administration groups were prepared according to the concentrations of ethyl alcohol, in which each group included 6 male ICR rats (6 weeks). 25

The toosendan fructus ethyl alcohol extract obtained in Example 9-1 was dissolved in 10% Labrasol (Gate Fosse Inc., France) as an excipient, and orally administered to a rat once a day. Extracts of ethyl alcohol with respective concentrations were administered to each group in doses of 1,000, 1,500, and 2000 mg / kg. 30

On the day of administration, the general symptoms were observed with an interval of one hour for 6 hours from the administration. Then, during the days after administration, general symptoms were observed and recorded once a day. Twice a week, the animal was weighed on the weighting day. After the end of the administration, the animal was fasted overnight, and then its blood was drawn, and underwent a biochemical examination. After blood collection, the animal underwent an autopsy, and no abnormal findings were observed in the main organs.

For the animals in each group, the average weight was recorded according to the days of measurement and mortality, and then MTD and NOAEL were obtained from the test sample. In order to determine if there was a difference in the average weight and blood biochemical value between a control group and the administration groups, a Dunnett's test was performed as a multiple comparison method, and a region was established Critical for the 5% test (* P <0.05).

BAT refers to a minimum dose of a test material administered to a test animal that will cause toxicity symptoms with no effect on its death, and an increase / decrease in weight by 10% or less with respect to a control group. NOAEL denotes the highest level of exposure in a toxicity test, in which there is no detrimental effect of the material administered in the long term.

As a result, as indicated in Table 1, since the content of ethyl alcohol was reduced in the extraction, the NOAEL was increased. It was also found that in the 30% ethyl alcohol extract, there was no toxicity, even at the maximum dose of 2000 mg / kg.

Table 1

MTD and NOAEL results according to extraction solvents

Ethyl alcohol extract

BAT (mg / kg) NOAEL (mg / kg)

100% ethyl alcohol

<1,000 500 - 750

70% ethyl alcohol

> 2,000 <1,000

50% ethyl alcohol

> 2,000 1,000 - 1,500

30% ethyl alcohol

> 2,000> 2,000

<9 - 3> Efficacy comparison test according to the types of extraction solvents of an extract of ethyl alcohol from toosendan fructus

In the ethyl alcohol extract of toosendan fructus obtained in Example 9-1, a reducing effect of PPAβ production, a favorable effect of PPAα production, and an inhibitory effect of Aβ production were measured in the same manner to that described in Example 5.

As a result, as shown in Figure 10, it was discovered that the cinnamon extract used in the present invention obtained from 100%, 70%, 50% and 30% ethyl alcohols as extraction solvent are excellent both in the reducing effect of the production of PPAβ as of the favoring effect of the production PPAα. In addition, as shown in Figure 11, it was found that the inhibitory effect of Aβ was generally high, although extraction by 30% ethyl alcohol reduced the efficiency by 14%.

Accordingly, when the cinnamon extract used in the present invention was extracted by ethyl alcohol as the extraction solvent, it is possible to achieve high efficiency in general regardless of the concentration of ethyl alcohol. Especially, it was found that when the content of ethyl alcohol used as an extraction solvent was adjusted in a range of 30% to 50%, it was possible to maintain efficacy and highly reduce the toxicity of the cinnamon extract used in the present invention.

Although examples of formulation of a pharmaceutical composition for use according to the present invention including the compound of the present invention are described, these specifically illustrate the invention and are not intended to limit it.

<Preparation Example 1>

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Powder preparation

toosendan fructus extract 20 mg

lactose 100 mg

talc 10 mg 30

After mixing the above ingredients and filling an airtight bag, they were prepared in powder form.

<Preparation Example 2>

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Tablet preparation

toosendan fructus extract 10 mg

100 mg corn starch

lactose 100 mg 40

magnesium stearate 2 mg

After mixing the above ingredients and performing direct compression, they were prepared in tablets according to a well known method.

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<Preparation Example 3>

Capsule Preparation

extract of meliae cortex 10 mg 50

3 mg crystallized cellulose

lactose 14.8 mg

0.2 mg magnesium stearate

After mixing the above ingredients and filling a gelatin capsule, they were placed in the capsule according to a well known method.

<Preparation Example 4>

Injection Preparation 60

The active ingredient was dissolved in distilled water for injection according to a well known method, and the pH was adjusted to 7.5 and then the above ingredient was dissolved in distilled water for injection. A 2 ml ampoule is then filled, sterilized and the injection prepared.

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toosendan fructus extract 1 mg

Mannitol 180 mg

water for injection 2793 mg

Na2HPO412H2O 26 mg

A blister (2 ml) was prepared by the above ingredients according to a well known method. 5

<Preparation Example 5>

Fluid Preparation

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toosendan fructus extract 2 mg

10 mg isomerized glucose syrup

mannitol 5 mg

appropriate distilled water

According to a well known method, all the ingredients are dissolved in distilled water and lemon flavor is added, then mixed and the volume is adjusted to 100 ml by adding distilled water. After adjustment, it is packaged in brown bottles and sterilized.

Industrial Applicability 20

As can be seen in the foregoing, a pharmaceutical composition for use according to the present invention comprising cinnamon extract, toosendanine, or a pharmaceutically acceptable salt thereof is an active ingredient very effective in the prevention or treatment of dementia. Especially, the composition for use according to the present invention is effective in inhibiting production and inducing the improvement of PPAα production that shows a protective effect of an Aβ nerve cell. Therefore, the pharmaceutical composition for use according to the present invention comprising cinnamon extract, toosendanine, or a pharmaceutically acceptable salt thereof as an active ingredient, is highly effective in various fields such as drug preparation / preventive treatment of patients. with dementia or people of ages susceptible to dementia. 30

Claims (10)

Hide Dependent

translated from Spanish

1. A composition for use in the prevention or treatment of dementia comprising toosendanine represented by formula 1 or a pharmaceutically acceptable salt thereof as an active ingredient. [Formula 1] image 1 2. The composition for use in the prevention or treatment of dementia according to claim 1, wherein the dementia is selected from the group consisting of: Alzheimer's dementia, cerebrovascular dementia, senile dementia, and dementia due to brain lesions. 3. Use of toosendanine represented by formula 1 or a pharmaceutically acceptable salt thereof to prepare an agent for the prevention or treatment of dementia. 10 4. The use of claim 3, wherein the dementia is selected from the group consisting of: Alzheimer's dementia, cerebrovascular dementia, senile dementia, and dementia from brain lesions. 5. A composition for use in the prevention or treatment of dementia comprising cinnamon extract (Melia azedarach or Melia toosendan) as an active ingredient. 6. The composition for use in the prevention or treatment of dementia according to claim 5, wherein the cinnamon is toosendan fructus (fruit of the cinnamon) or Meliae cortex (candle or cinnamon bark). twenty 7. The composition for use in the prevention or treatment of dementia according to claim 5, wherein the extract is extracted with ethyl acetate or water, C1 to C6 alcohol or a mixed solvent thereof. 8. The composition for use in the prevention or treatment of dementia according to claim 5, wherein the dementia is selected from the group consisting of: Alzheimer's dementia, cerebrovascular dementia, senile dementia, and dementia due to brain lesions. 9. Use of cinnamon extract (Melia azedarach or Melia toosendan) to prepare an agent for the prevention or treatment of dementia. 30 10. The use of claim 9, wherein the dementia is selected from the group consisting of: Alzheimer's dementia, cerebrovascular dementia, senile dementia, and dementia from brain lesions.

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KR20220076375A2022-06-08A novel pharmaceutical composition for treating neurodegenerative disease

Priority And Related Applications

Applications Claiming Priority (3)

ApplicationFiling dateTitle

KR200900549492009-06-19

KR1020090054949A2009-06-19Composition for preventing or treating dementia comprising toosendanin or extracts of Melia azedarach(Melia toosendan)

PCT/KR2010/0039712010-06-18Use of toosendanin or melia azedarach extracts for preventing or treating dementia

Concepts

machine-extracted

DownloadFilter table

NameImageSectionsCountQuery match

Dementiatitle,claims,abstract,description810.000

preventiontitle,claims,abstract,description300.000

extracttitle,claims,description1010.000

Melia azedarachtitle,claims,description500.000

Toosendanintitle,description310.000

Toosendanintitle,description310.000

toosendanintitle,description310.000

mixtureclaims,abstract,description390.000

active ingredientclaims,abstract,description250.000

sodium chlorideclaims,abstract,description240.000

saltsclaims,abstract,description230.000

cinnamon extractclaims,description350.000

acetic acid ethyl esterclaims,description330.000

Alzheimer's diseaseclaims,description250.000

Cinnamomum zeylanicumclaims,description210.000

Cinnamomum zeylanicumclaims,description200.000

cinnamonclaims,description200.000

waterclaims,description180.000

edible fruitsclaims,description80.000

chemical substances by applicationclaims,description70.000

Senile dementiaclaims,description60.000

1-Hexanolclaims,description30.000

Canella winteranaclaims,description30.000

Canella winteranaclaims,description30.000

Cinnamon Barkclaims,description30.000

mixed solventclaims,description30.000

Eucalyptus rubidaclaims,description20.000

Eucalyptus rubidaclaims,description20.000

Central nervous system lesionclaims40.000

Show all concepts from the description section