However, the above patent document neither discloses nor suggests the effects of verbenone derivatives on the reduction of neuronal death and oxidative stress, the inhibition of ischemic brain injury and the inhibition of migration of inflammatory cells.

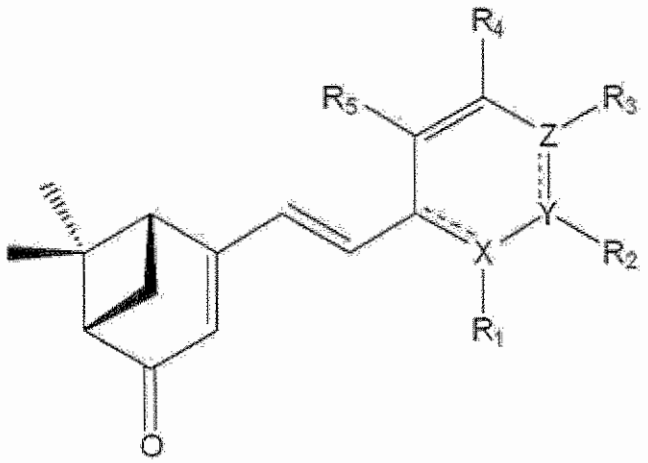
Accordingly, the present inventors have measured NMDA-induced excitotoxicity and cell death in a hypoxic-ischemic rat model in order to examine the effects of verbenone derivatives on the reduction of neuronal death and oxidative stress and the inhibition of ischemic brain injury and inflammatory responses, and performed an experiment on the antioxidant activities of verbenone derivatives. As a result, the present inventors have first found that verbenone derivatives have an effect on the treatment of degenerative brain diseases. More specifically, the present inventors have found that verbenone derivatives according to the present invention reduce neuronal death and oxidative stress, and exhibit excellent effects on the inhibition of ischemic brain injury and inflammatory responses *in vivo*, thereby completing the present invention.

DISCLOSURE ~~OF INVENTION~~

The object of the present ~~invention~~ disclosure is to provide the novel use of a verbenone derivative for preventing or treating a degenerative brain disease.

To achieve the above object, the present ~~invention~~ disclosure provides a pharmaceutical composition for preventing or treating a degenerative brain disease, the composition comprising, as an active ingredient, a verbenone derivative having a structure of Formula 1 or a pharmaceutically acceptable salt thereof:

Formula 1



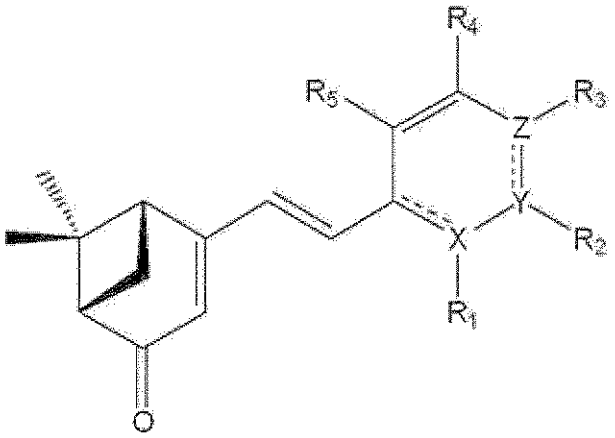
wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from a hydrogen atom, a halogen atom selected from among F, Cl, Br and I, a hydroxyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkoxy group, an amino group, a C_1-C_3 alkylamine group, a C_1-C_3 alkyldiamine group, a C_5-C_8 aromatic ring, a C_5-C_8 cyclic ring, and a C_5-C_8 heteroaromatic ring; X, Y and Z are each independently a carbon atom or at least one

heteroatom selected from the group consisting of N, O and S atoms; and

denotes a double bond or a single bond.

In one aspect, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for the prevention or treatment of a degenerative brain disease, wherein the pharmaceutical composition comprises a verbenone derivative represented by a following Formula 1 or a pharmaceutically acceptable salt thereof, as an active ingredient:

Formula 1



wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen atom, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkoxy group, an amino group, a C_1-C_3 alkylamine group, a C_1-C_3 alkyldiamine

group, a C_5-C_8 aromatic ring, a C_5-C_8 cyclic ring, and a C_5-C_8 heteroaromatic ring;

X, Y and Z are each independently a carbon atom or at least one heteroatom selected from the group consisting of N, O and S atoms; and

~~dotted~~

denotes a double bond or a single bond.

In the present ~~invention~~disclosure, the mentioned verbenone derivative may function to reduce neuronal death and oxidative stress, inhibit ischemic brain injury, and inhibit the migration of inflammatory cells.

In the present ~~invention~~disclosure, the degenerative brain disease may be stroke, palsy, dementia, Alzheimer's disease, Parkinson's disease, or Huntington's disease. Specifically, it may be stroke, vascular dementia, or dementia of Alzheimer type. More specifically, it may be stroke, and even more specifically ischemic stroke disease.

In the present ~~invention~~disclosure, the composition may further contain a suitable carrier, excipient or diluent that is generally used in the preparation of pharmaceutical compositions.

In the present ~~invention~~disclosure, the composition may be formulated or used in combination with one or more drugs selected from the group consisting of calcium channel blockers, antioxidants, glutamate antagonists, anticoagulants, antihypertensive drugs, antithrombotic drugs, antihistamines, anti-inflammatory drugs, anticancer drugs, and antibiotics.

The present ~~invention~~ disclosure also provides the use of a verbenone derivative having a structure of Formula 1 or a pharmaceutically acceptable salt thereof for preventing or treating a degenerative brain disease.

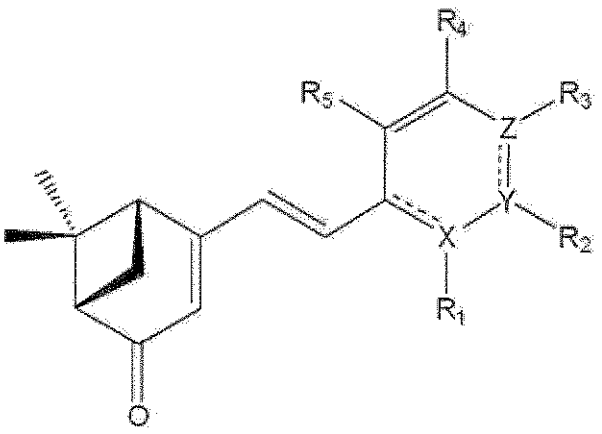
The present ~~invention~~ disclosure also provides a method of preventing or treating a degenerative brain disease using a verbenone derivative having a structure of Formula 1 or a pharmaceutically acceptable salt thereof.

The present ~~invention~~ disclosure also provides a method for preventing or treating a degenerative brain disease, the method comprising administering to a subject a verbenone derivative having a structure of Formula 1 or a pharmaceutically acceptable salt thereof.

The present ~~invention~~ disclosure also provides a functional food for preventing or alleviating a degenerative brain disease, the food comprising, as an active ingredient, a verbenone derivative having a structure of Formula 1.

In one aspect, there is provided the use of a health functional food in the manufacture of a medicament for the prevention or improvement of a degenerative brain disease, wherein the health functional food comprises a verbenone derivative represented by a following Formula 1 or a pharmaceutically acceptable salt thereof, as an active ingredient:

Formula 1



wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen atom, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkoxy group, an amino group, a C_1-C_3 alkylamine group, a C_1-C_3 alkyldiamine group, a C_5-C_8 aromatic ring, a C_5-C_8 cyclic ring, and a C_5-C_8 heteroaromatic ring;

X, Y and Z are each independently a carbon atom or at least one heteroatom selected from the group consisting of N, O and S atoms; and

denotes a double bond or a single bond.

BRIEF DESCRIPTION OF THE DRAWINGS

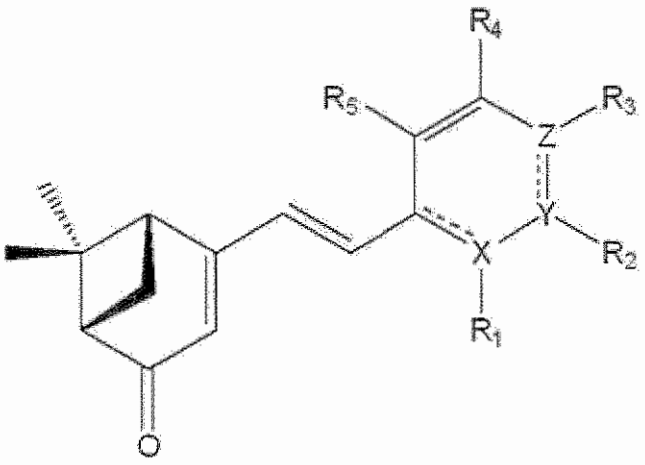
FIG. 1 shows the effects of compound derivatives of the present invention on the protection of rat cortical neuronal cells.

FIG. 2 shows the effects of compound derivatives of the present invention against NMDA-induced excitotoxicity.

WHAT IS CLAIMED IS:

1. ~~A~~Use of a pharmaceutical composition in the manufacture of a medicament for the prevention or treatment of~~for preventing or treating~~ a degenerative brain disease, ~~comprising~~ wherein the pharmaceutical composition comprises a verbenone derivative represented by a following Formula 1 or a pharmaceutically acceptable salt thereof, as an active ingredient:

Formula 1



wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen atom, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkoxy group, an amino group, a C_1-C_3 alkylamine group, a C_1-C_3 alkyldiamine group, a C_5-C_8 aromatic ring, a C_5-C_8 cyclic ring, and a C_5-C_8 heteroaromatic ring;

X, Y and Z are each independently a carbon atom or at least one heteroatom selected from the group consisting of N, O and S atoms; and

⋯⋯ denotes a double bond or a single bond.

2. The ~~pharmaceutical composition~~use of claim 1, wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen atom, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a methyl group, an ethyl group, a methoxy group, an ethoxy group, an amino group, a C_5-C_6 aromatic ring, a C_5-C_6 cyclic ring, and a C_5-C_6 heteroaromatic ring.

3. The ~~pharmaceutical composition~~use of claim 2, wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen atom, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a methyl group, a methoxy group, a phenyl group, a pyrrole group, and a pyridine group.

4. The ~~pharmaceutical composition~~use of claim 1, wherein the X, Y and Z are each independently a carbon atom or at least one heteroatom selected from the group consisting of N, O and S atoms.

5. The ~~pharmaceutical composition~~use of claim 4, wherein the X, Y and Z are each independently at least one atom selected from the group consisting of a carbon atom and an N atom.

6. The ~~pharmaceutical composition~~use of claim 1, wherein the composition comprises a compound selected from the group consisting of:

(1*S*,5*R*)-4-(4-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3a);

(1*S*,5*R*)-4-(4-hydroxy-2-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3b);

(1*S*,5*R*)-4-(3,4-dihydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3c);

(1*S*,5*R*)-4-(3-bromo-4-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3d);

(1*S*,5*R*)-4-(4-hydroxy-2,6-dimethoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3e);

(1*S*,5*R*)-4-(3,4-dihydroxy-5-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3f);

(1*S*,5*R*)-4-(3-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3g);

(1*S*,5*R*)-4-(2-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3h);

(1*S*,5*R*)-4-(2-hydroxy-4-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3i);

(1*S*,5*R*)-6,6-dimethyl-4-styryl-bicyclo[3.1.1]hept-3-en-2-one (4a);

(1*S*,5*R*)-4-(4-fluorostyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4b);

(1*S*,5*R*)-4-(4-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4c);

(1*S*,5*R*)-4-(2-(biphenyl-4-yl)vinyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4d);

(1*S*,5*R*)-4-(4-(1H-pyrrol-1-yl)styryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4e);

(1*S*,5*R*)-4-(3,4-dimethoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4f);

(1*S*,5*R*)-4-(3,5-dimethoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4g);

(1*S*,5*R*)-4-(2,5-dimethoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4h);

(1*S*,5*R*)-4-(5-bromo-2-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4i);

(1*S*,5*R*)-6,6-dimethyl-4-((E)-2-(pyridin-2-yl)vinyl)-bicyclo[3.1.1]hept-3-en-2-one (5a);

(1*S*,5*R*)-6,6-dimethyl-4-((E)-2-(pyridin-3-yl)vinyl)-bicyclo[3.1.1]hept-3-en-2-one (5b); and

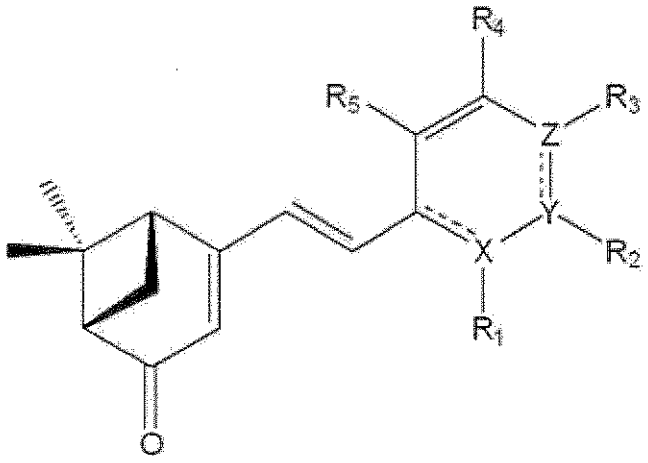
(1*S*,5*R*)-6,6-dimethyl-4-((E)-2-(pyridin-4-yl)-vinyl)-bicyclo[3.1.1]hept-3-en-2-one (5c).

7. The ~~pharmaceutical composition~~use of claim 1, wherein the degenerative brain disease is stroke, palsy, dementia, Alzheimer's disease, Parkinson's disease, or Huntington's disease.

8. The ~~pharmaceutical composition~~use of claim 1, wherein the degenerative brain disease is stroke.

9. Use of a~~A~~ health functional food in the manufacture of a medicament for the prevention or improvement of ~~for preventing or improving~~ a degenerative brain disease, ~~comprising~~ wherein the health functional food comprises a verbenone derivative represented by a following Formula 1 or a pharmaceutically acceptable salt thereof, as an active ingredient:

Formula 1



wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen atom, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkoxy group, an amino group, a C_1-C_3 alkylamine group, a C_1-C_3 alkyldiamine group, a C_5-C_8 aromatic ring, a C_5-C_8 cyclic ring, and a C_5-C_8 heteroaromatic ring;

X, Y and Z are each independently a carbon atom or at least one heteroatom selected from the group consisting of N, O and S atoms; and

 denotes a double bond or a single bond.

10. The ~~health functional food~~use of claim 9, wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen atom, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a methyl group, an ethyl group, a methoxy group, an ethoxy group, an

amino group, a C_5-C_6 aromatic ring, a C_5-C_6 cyclic ring, and a C_5-C_6 heteroaromatic ring.

11. The ~~health functional food~~use of claim 10, wherein R_1, R_2, R_3, R_4 and R_5 are each independently at least one selected from the group consisting of a hydrogen, a halogen atom selected from F, Cl, Br and I, a hydroxyl group, a methyl group, a methoxy group, a phenyl group, a pyrrole group, and a pyridine group.

12. The ~~health functional food~~use of claim 9, wherein the X, Y and Z are each independently a carbon atom or at least one heteroatom selected from the group consisting of N, O and S atoms.

13. The ~~health functional food~~use of claim 12, wherein the X, Y and Z are each independently at least one atom selected from the group consisting of a carbon atom and an N atom.

14. The ~~health functional food~~use of claim 9, wherein the composition comprises a compound selected from the group consisting of:

(1S,5R)-4-(4-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3a);

(1S,5R)-4-(4-hydroxy-2-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3b);

(1S,5R)-4-(3,4-dihydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3c);

(1S,5R)-4-(3-Bromo-4-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3d);

(1S,5R)-4-(4-hydroxy-2,6-dimethoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3e);

(1S,5R)-4-(3,4-dihydroxy-5-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3f);

(1S,5R)-4-(3-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3g);

(1S,5R)-4-(2-hydroxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3h);

(1S,5R)-4-(2-hydroxy-4-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (3i);

(1S,5R)-6,6-dimethyl-4-styryl-bicyclo[3.1.1]hept-3-en-2-one (4a);

(1S,5R)-4-(4-fluorostyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4b);

(1S,5R)-4-(4-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4c);

(1S,5R)-4-(2-(biphenyl-4-yl)vinyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (4d);

(1S,5R)-4-(4-(1H-pyrrol-1-yl)styryl)-6,6-dimethylbicyclo [3.1.1]hept-3-en-2-one (4e);

(1S,5R)-4-(3,4-dimethoxystyryl)-6,6-dimethylbicyclo [3.1.1]hept-3-en-2-one (4f);

(1S,5R)-4-(3,5-dimethoxystyryl)-6,6-dimethylbicyclo [3.1.1]hept-3-en-2-one (4g);

(1S,5R)-4-(2,5-dimethoxystyryl)-6,6-dimethylbicyclo [3.1.1]hept-3-en-2-one (4h);

(1S,5R)-4-(5-bromo-2-methoxystyryl)-6,6-dimethyl bicyclo[3.1.1]hept-3-en-2-one (4i);

(1S,5R)-6,6-dimethyl-4-((E)-2-(pyridin-2-yl)vinyl)-bicyclo[3.1.1]hept-3-en-2-one (5a);

(1S,5R)-6,6-dimethyl-4-((E)-2-(pyridin-3-yl)vinyl)-bicyclo[3.1.1]hept-3-en-2-one (5b); and

(1S,5R)-6,6-dimethyl-4-((E)-2-(pyridin-4-yl)-vinyl)-bicyclo[3.1.1]hept-3-en-2-one (5c).

15. The ~~health functional food~~use of claim 9, wherein the degenerative brain disease is stroke, palsy, dementia, Alzheimer's disease, Parkinson's disease, or Huntington's disease.

16. The ~~health functional food~~use of claim 15, wherein the degenerative brain disease is stroke.