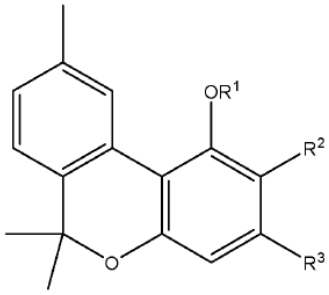
[0014] Cannabinoids, and derivatives thereof, have several properties with therapeutic potential. Activation or blocking of CB1 and/or CB2 receptors with a cannabinoid can regulate downstream signaling and metabolic pathways and subsequently influence synaptic transmission, including transmission of pain and other sensory signals in the periphery, immune response, and inflammation. Thus, there is an interest in the use of natural or synthetic cannabinoids for therapeutic purposes. However, despite anecdotal reports of cannabinoid therapeutic effects, many cannabinoids and their derivatives have been demonstrated to exhibit no detectable neuroprotective effect at physiological concentrations. Moreover, some cannabinoids and their derivatives have been shown to contribute to excitotoxicity at physiological concentrations.

SUMMARY

[0015] Described herein are neuroprotective compositions and formulations, and methods of their making and use. A neuroprotective composition, or a formulation containing a neuroprotective composition, can be contacted with a neuron, thereby providing a neuroprotective effect. In certain examples, the contacting is performed by administering the neuroprotective composition, or a formulation containing the composition, to a subject in need thereof. The neuroprotective compositions, formulations, and related methods are useful in treating a wide variety of neurodegenerative diseases. In certain examples, neuroprotective compositions are provided for use in inducing a neuroprotective effect in retinal neurons. For example, a neuroprotective composition can be locally or systemically administered to a subject to induce a neuroprotective effect in retinal neurons, e.g., to treat an optical neurodegenerative disease such as glaucoma or inhibit neurodegeneration associated with diabetic retinopathy, AMD, and/or retinitis pigmentosa.

[0015a] In one aspect, the present disclosure refers to a use of a composition comprising a neuroprotective compound in an amount sufficient to inhibit neurodegeneration in the manufacture of a medicament for protecting a retinal neuron from neurodegeneration, wherein the composition is to be contacted with the retinal neuron, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

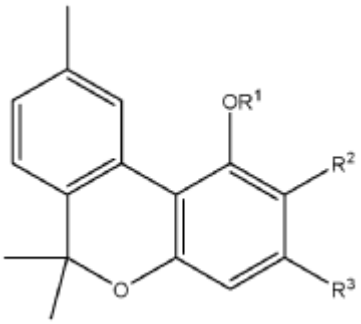
or a derivative thereof;

wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration:

of from 0.15 µM to less than 15 µM of the neuroprotective compound in contact with a target retinal neuron.

[0015b] In another aspect, the present disclosure refers to a use of a composition comprising a neuroprotective compound as described herein, in the manufacture of a medicament for the treatment of neurodegeneration in a subject in need thereof.

[0015c] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a neuroprotective compound in an eye drop formulation, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*- C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

or a derivative thereof.;

wherein the neuroprotective compound is in amount sufficient to achieve a concentration of from 0.15 µM to less than 15 µM of the neuroprotective compound in contact with a target retinal neuron.

[0015d] In another aspect, the present disclosure refers to the composition comprising neuroprotective compound as described herein for use in therapy.

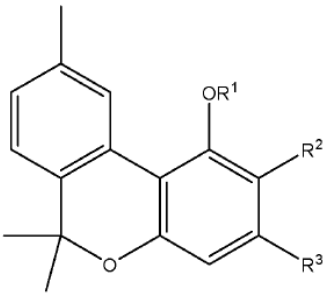
[0016] In one example, the present disclosure provides a method of protecting a neuron from neurodegeneration, the method comprising contacting the neuron with a composition comprising cannabinol, or a derivative thereof, in an amount sufficient to inhibit neurodegeneration. In some examples, the contacting is *in vitro*. In some examples, the contacting is *in vivo*. In some examples, the contacting comprises administering the composition to a subject in need thereof. In some examples, the neuron is a retinal neuron (e.g., retinal ganglion).

[0017] In some examples, the contacting comprises topically administering the composition to a subject in need thereof. For example, administering the composition to a

CLAIMS

What is claimed is:

1. Use of a composition comprising a neuroprotective compound in an amount sufficient to inhibit neurodegeneration in the manufacture of a medicament for protecting a retinal neuron from neurodegeneration, wherein the composition is to be contacted with the retinal neuron, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

or a derivative thereof~~.~~;

wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration:

of from 0.15 µM to less than 15 µM of the neuroprotective compound in contact with a target retinal neuron.

2. The use of claim 1, wherein the composition is to be administered to a subject in need thereof.

~~3. The use of claim 1 or 2, wherein the neuron is a retinal neuron.~~

3~~4~~. The use of claim 2~~ or 3~~, wherein the composition is to be administered to a subject in need thereof and the subject is suffering from a neurodegenerative disease.

4~~5~~. The use of claim 3~~4~~, wherein neurodegenerative disease is a neurodegenerative disease affecting the eye, preferably wherein the neurodegenerative disease is selected from the group consisting of glaucoma, age-related macular degeneration (AMD) retinitis pigmentosa, and diabetic retinopathy.

5~~6~~. The use of claim 3~~4~~, wherein neurodegenerative disease is glaucoma.

6~~7~~. The use of claim 5~~6~~, wherein the composition is to be administered simultaneously or sequentially with an additional active agent for treatment of the glaucoma.

7~~8~~. The use of any one of claims 1 to 6~~7~~, wherein the amount sufficient to inhibit neurodegeneration is an amount sufficient to reduce an amount or rate of apoptosis of a population of retinal neurons contacted with the composition.

8~~9~~. The use of any one of claims 1 to 7~~8~~, wherein the retinal neuron is subject to elevated hydrostatic pressure and the retinal neuron is to be contacted with the composition comprising the neuroprotective compound in an amount sufficient to reduce pressure-induced neurodegeneration.

9~~10~~. The use of any one of claims 1 to 8~~9~~, wherein the composition comprising the neuroprotective compound is provided in a microemulsion.

10~~11~~. The use of any one of claims 1 to 8~~9~~, wherein the composition comprising the neuroprotective compound is provided in an extended release formulation.

11~~12~~. The use of claim 10~~11~~, wherein the formulation comprises:

a. a delivery carrier comprising a cellulosic polymer and an anionic polysaccharide; and

b. nanoparticles comprising an amphiphilic non-ionizable block copolymer and the neuroprotective compound,

wherein the formulation has a gel point of ~~about~~ 30 ~~-~~°C to ~~about~~ 37 ~~-~~°C.

~~13. The use of any one of claims 1 to 12, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from about 0.15 μM to less than about 15 μM of the neuroprotective compound in contact with the neuron.~~

12~~14~~. The use of claim 11~~13~~, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of greater than ~~about~~ 0.5 μM and less than 15 μM of the neuroprotective compound in contact with the retinal neuron.

13~~15~~. The use of claim 11~~14~~, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from ~~about~~ 0.5 μM to less than 15 μM of the neuroprotective compound, preferably from greater than ~~about~~ 0.5 μM to less than 12 μM of the neuroprotective compound in contact with the retinal neuron.

14~~16~~. The use of claim 11~~15~~, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from ~~about~~ 1.5 μM to 10 μM of the neuroprotective compound in contact with the retinal neuron.

15~~17~~. The use of any one of claims 1 to 14~~16~~, wherein the composition comprising the neuroprotective compound is to be administered systemically.

16~~18~~. The use of claim 15~~17~~, wherein the systemic administration comprises intravenous injection.

17~~19~~. The use of any one of claims 1 to 14,~~16~~ wherein the composition comprising the neuroprotective compound is to be administered locally.

18~~20~~. The use of any one of claims 1 to 14~~16~~, wherein the composition comprising the neuroprotective compound is to be administered directly to the eye.

19~~21~~. The use of claim 18~~20~~, wherein the neuroprotective compound in an eye drop formulation is to be administered to the eye.

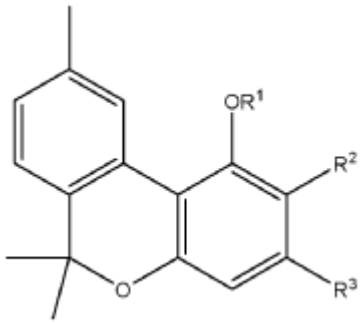
20~~22~~. The use of claim 19~~21~~, wherein the eye drop formulation is to be administered weekly, daily, or twice daily.

21~~23~~. The use of any one of claims 1 to 20~~22~~, wherein the neuroprotective compound is cannabinol, or cannabinolic acid, or a prodrug thereof.

22~~24~~. The use of claim 21~~23~~, wherein the neuroprotective compound is cannabinol.

23~~25~~. Use of a composition comprising a neuroprotective compound as defined in claim 1, in the manufacture of a medicament for the treatment of neurodegeneration in a subject in need thereof.

24~~26~~. A pharmaceutical composition comprising a neuroprotective compound in an eye drop formulation, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*- C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

or a derivative thereof~~.~~:

wherein the neuroprotective compound is in amount sufficient to achieve a concentration of from 0.15 µM to less than 15 µM of the neuroprotective compound in contact with a target retinal neuron.

25~~27~~. The pharmaceutical composition of claim 24~~26~~, wherein the neuroprotective compound is present at a concentration of from 0.1% w/w to 0.5% w/w.

26~~28~~. The pharmaceutical composition of claim 24 or 25~~26 or 27~~, wherein the neuroprotective compound is cannabinol, or cannabinolic acid.

27~~29~~. The pharmaceutical composition of claim 24, 25, or 26, ~~26, 27, or 28,~~ wherein the neuroprotective compound is cannabinol.

~~30. The pharmaceutical composition of any one of claims 26 to 29, wherein the neuroprotective compound is in an amount sufficient to achieve a concentration of from about 0.15 µM to less than about 15 µM of the neuroprotective compound in contact with a target neuron.~~

28~~31~~. The pharmaceutical composition of any one of claims 24 to 27~~26 to 30~~, wherein the eye drop formulation is a microemulsion, or a hydrogel formulation.

29~~32~~. The pharmaceutical composition of claim 28~~31~~, wherein the eye drop formulation is a hydrogel formulation comprising: a) a delivery carrier comprising a cellulosic polymer and an anionic polysaccharide; and b) nanoparticles comprising an amphiphilic non-ionizable block copolymer and the neuroprotective compound, wherein the formulation has a gel point of ~~about~~ 30~~-~~°C to ~~about~~ 37~~-~~°C.

30~~33~~. The composition comprising neuroprotective compound of claim 1 for use in therapy.