[009] Leptin has been shown to alleviate neuropathic pain induced by chronic nerve injury [X. Li, *et al*., Mol. Pain (2013) 9:65].

[010] The inventors also have demonstrated that dicarboxylic acid esters induce a number of changes in cellular and organismal signaling that are therapeutically useful. In addition to their other pharmacological activities, dicarboxylic acid esters induce the cellular release and/or production of signaling molecules that have analgesic properties. Responsive cellular molecules include leptin, macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor (GM-CSF). In addition, the inventors have discovered that treatment of mammalian cells and tissues with dicarboxylic acid esters can suppress the production of markers associated with pain, which include inducible nitric oxide synthase (iNOS) [Y. Kwok, *et al*., PLoS One. 2012;7(8):e44232], S-nitrosylated cysteine residues in cellular proteins [J. Zhang, *et al*., Int. Anesthesiol. Clin. (2007) 45(2):27-37], prostaglandin E2 (PGE2) [A. Ahlawat, *et al*., Eur. J. Pharmacol. (2018) 818:419-28], and adenosine triphosphate (ATP) [Mense, Dtsch Arztebl Int 2008; 105(12): 214–9].

SUMMARY OF THE INVENTION

[011] The present disclosure provides methods and pharmaceutical compositions including a dicarboxylic acid ester of Formula I: $R_2OOC\text{-}(CH_2)_n\text{-}COOR_1$, wherein n is between 4 and 10, and each R_1 and R_2 are independently a lower alkyl, for inducing an analgesic effect in a subject. Certain examples herein relate to inducing an analgesic effect in a subject, thereby inhibiting pain due to the activation of pattern recognition receptors (PRR) including Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD) receptors, and/or Dectin receptors.

[012] Certain examples herein relate to inducing an analgesic effect, thereby inhibiting a localized pain in a subject, by promoting the secretion of leptin, macrophage colony-stimulating factor (M-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), and/or granulocyte colony-stimulating factor (G-CSF).

[013] Examples herein relate to methods and pharmaceutical compositions including a dicarboxylic acid ester of Formula I for inducing an analgesic effect, thereby inhibiting a localized pain in a subject, by suppressing the expression and

secretion of prostaglandin E2 (PGE2) and/or inducible nitric oxide synthase (iNOS) and/or adenosine triphosphate (ATP).

[014] Examples herein relate to methods of inducing an analgesic effect, thereby inhibiting localized pain in a subject, the method including the step of administering to the subject in need a dicarboxylic acid ester of Formula I, wherein administration results in a reduction in a symptom associated with the pain condition.

[015] Examples herein relate to uses of a dicarboxylic acid ester of Formula I in the manufacture of a medicament for inducing an analgesic effect, thereby inhibiting localized pain in a subject.

[016] Examples herein relate to uses of a dicarboxylic acid ester of Formula I for inducing an analgesic effect, thereby inhibiting localized pain in a subject.

[017] Examples herein relate to uses of a dicarboxylic acid ester of Formula I in the manufacture of a medicament for inducing an analgesic effect in a subject, thereby inhibiting localized pain in a subject, such as acute pain, chronic pain, nociceptive pain, neuropathic pain, or nociplastic pain.

[018] Examples herein relate to uses of a dicarboxylic acid ester of Formula I in the manufacture of a medicament for inducing an analgesic effect in a subject, thereby inhibiting localized pain responsive to the modulation of one or more receptors in a subject in need selected from iNOS, ATP, and pattern recognition receptors (PRR) including Toll Like, NOD and Dectin receptors.

[019] Examples herein relate to uses of a dicarboxylic acid ester of Formula I in the manufacture of a medicament for inducing an analgesic effect, thereby inhibiting localized pain in a subject, by upregulating the activity and/or expression of one or more of leptin, M-CSF, G-CSF, and GM-CSF, or downregulating the activity and/or expression or release of at least one of ATP, iNOS and PGE2.

[019a] In one aspect, the present disclosure provides use of diethyl azelate in the manufacture of a medicament for inducing a localized analgesic effect in a subject suffering from pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, nociplastic pain, traumatic pain, chemical pain, burn pain, ischemic pain, insect bite pain, prickling pain, musculoskeletal pain, rheumatoid or osteoarthritis pain, post-surgical pain, bone pain, and skin-related painwherein the diethyl azelate is present in an amount of from 20% to 100% by weight of the medicament, and wherein a therapeutically effective amount of the diethyl azelate is to be administered topically to the subject.

[019b] In another aspect, the present disclosure provides use of a formulation in the manufacture of a medicament for inducing a localized analgesic effect in a subject suffering from pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, nociplastic pain, traumatic pain, chemical pain, burn pain, ischemic pain, insect bite pain, prickling pain, musculoskeletal pain, rheumatoid or osteoarthritis pain, post-surgical pain, bone pain, and skin-related pain, wherein the formulation comprises:

from 20% to about 100% by weight of the formulation of a therapeutically effective amount of diethyl azelate; and

a pharmaceutically acceptable carrier;

and wherein the formulation is to be administered topically to the subject.

DESCRIPTION OF THE DRAWINGS

CLAIMS

What is claimed is:

1. Use of diethyl azelate in the manufacture of a medicament for inducing a localized analgesic effect in a subject suffering from pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, nociplastic pain, traumatic pain, chemical pain, burn pain, ischemic pain, insect bite pain, prickling pain, musculoskeletal pain, rheumatoid or osteoarthritis pain, post-surgical pain, bone pain, and skin-related painwherein the diethyl azelate is present in an amount of from 20% to 100% by weight of the medicament, and wherein a therapeutically effective amount of the diethyl azelate is to be administered topically to the subject.

2. The use of claim 1, wherein inducing the localized analgesic effect is accomplished by disrupting a lipid raft of the subject by the dicarboxylic acid ester.

3. The use of claim 2, wherein the lipid raft comprises monosialotetrahexosylganglioside1 (GM1).

4. The use of claim 2, wherein the lipid raft comprises phospholipase D2 (PLD2).

5. The use of claim 2, wherein the disrupting of the lipid raft membrane results from the increase of the plasma membrane fluidity.

6. The use of claim 1, wherein inducing the localized analgesic effect, thereby inhibiting pain in the subject, comprises activating one or more receptors selected from the group consisting of pattern recognition receptors (PRR), nucleotide oligomerization domain (NOD) receptors, and Dectin receptors.

7. The use of claim 1, wherein inducing the analgesic effect, thereby inhibiting pain in the subject, comprises promoting the synthesis or release of the activity and/or expression of one or more of leptin, macrophage colony-stimulating

factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF).

8. The use of claim 1, wherein inducing the localized analgesic effect, thereby inhibiting pain in the subject, comprises inhibiting the synthesis or release of the activity and/or expression of at least one of adenosine triphosphate (ATP), inducible nitric oxide synthase (iNOS) and prostaglandin E2 (PGE2).

9. The use of claim 1, wherein the administration is to be performed at every 4 to 8 hours.

10. The use of claim 1, wherein the administration is for a duration of from 1 day to 30 days.

11. The use of claim 1, wherein the subject is a human.

12. Use of a formulation in the manufacture of a medicament for inducing a localized analgesic effect in a subject suffering from pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, nociplastic pain, traumatic pain, chemical pain, burn pain, ischemic pain, insect bite pain, prickling pain, musculoskeletal pain, rheumatoid or osteoarthritis pain, post-surgical pain, bone pain, and skin-related pain, wherein the formulation comprises:

from 20% to about 100% by weight of the formulation of a therapeutically effective amount of diethyl azelate; and

a pharmaceutically acceptable carrier;

and wherein the formulation is to be administered topically to the subject.