Specifically, IL-1β is translated in macrophages during NLRP3 activation as an inactive pro-protein that is cleaved by caspase-1 and secreted as the pro-inflammatory cytokine (Lopez-Castejon and Brough, 2011). The inflammatory cytokine IL-1β is a master regulator of inflammation and controls diverse inflammatory phenotypes at the cellular level including the recruitment activation of immune cells, the release of inflammatory signals such as nitric oxide and chemokines, as well as mediating gross metabolic and physiologic changes associated with inflammation such as fever and cortisol release. IL-1β is also linked with diseases associated with chronic sterile inflammation (Dinarello, 2011).

[0010] Due to the prevalence of diseases and health condition involving chronic sterile inflammation, there is great need for therapeutic drugs that can inhibit inflammation without resulting in severe or complicating side effects. There is a particular need for new therapeutics that can be used to safely treat a disease state involving sterile inflammation for long periods of time.

[0011] It will be clearly understood that, if a prior art publication is referred to herein, this reference does not constitute an admission that the publication forms part of the common general knowledge in the art in Australia or in any other country.

SUMMARY

[0011a] In a first aspect, the present disclosure refers to a composition comprising one or more natural products selected from the group consisting of compounds that can be isolated from plants of the genera *Withania* present within the concentration range of 3-350 nM; one or more omega-3 fatty acids present within the concentration range of 1340 nM – 85 µM, and:

(i) an extract of turmeric (from plants of *Curcuma longa*) present within the concentration range of 99 nM – 21 µM; or

(ii) an extract of pepper (from plants of *Piper nigrum*) present within the concentration range of 135 nM – 410 µM; or

(iii) an extract of turmeric (from plants of *Curcuma longa*) present within the concentration range of 99 nM – 21 µM, and an extract of pepper (from plants of *Piper nigrum*) present within the concentration range of 135 nM – 410 µM;

wherein the combination of one or more omega-3 fatty acids, and extracts from *Withania*, turmeric and/or pepper is a synergistic combination,

wherein the synergistic combination is within a low dose range of up to Fa 0.65.

[0011b] In another aspect, the present disclosure refers to a composition disclosed herein, for use in protecting a subject from sterile inflammation.

[0011c] In yet another aspect, the present disclosure refers to a composition disclosed herein, for use in treating and/or preventing a condition associated with sterile inflammation.

[0011d] In a further aspect, the present disclosure refers to a use of withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), piperine (derived from *Piper nigrum*), and one or more omega-3 fatty acids in the manufacture of a medicament for protecting a subject from sterile inflammation.

[0011e] In another aspect, the present disclosure refers to a use of withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), piperine (derived from *Piper nigrum*), and one or more omega-3 fatty acids in the manufacture of a medicament for treating and/or preventing a condition associated with sterile inflammation.

[0011f] In yet another aspect, the present disclosure refers to a use of a composition disclosed herein, in the manufacture of a medicament for protecting a subject from sterile inflammation.

[0011g] In a further aspect, the present disclosure refers to a use of a composition of any one of claims 1 to 10, in the manufacture of a medicament for treating and/or preventing a condition associated with sterile inflammation.

[0012] The present disclosure is directed to a composition for inhibiting inflammation, which may at least partially overcome at least one of the abovementioned disadvantages or provide the consumer with a useful or commercial choice.

[0013] With the foregoing in view, the present disclosure in one form, resides broadly in a composition comprising one or more natural products. Preferably, the composition comprises one or more natural products in a synergistic combination.

[0014] Preferably, the natural products are selected from compounds that can be isolated from cruciferous vegetables, compounds that can be isolated from plants of the genera *Withania*, *Brassica*, *Armoracia*, *Barbarea*, *Diplotaxis*, *Eruca*, *Lepidium*, *Nasturtium*, *Raphanus*, *Wasabia*, *Curcuma*, *Piper*, *Gardenia*, *Berberis*, *Silybum*, *Plectranthus, Vitis, Vaccinum, Rubus, Rheum,* or *Cannabis*, and compounds that can be isolated from various plants, including but not limited to rhubarb, buckthorn, Japanese knotweed, black pepper, and wheat germ.

[0015] In particularly preferred examples, the composition can comprise one or more natural products selected from the group consisting of withaferin A, sulforaphane, berteroin, genipin, berberine, resveratrol, emodin, piperine, spermidine, beta-hydroxybutyric acid, silybin, forskolin, indole-3-carbinol and cannabidiol.

[0016] Even more preferably, the composition comprises two or more compounds or extracts selected from withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), and piperine (derived from *Piper nigrum*).

[0017] In another example, the present disclosure resides broadly in a method of protecting a subject from sterile inflammation, the method comprising administering to the subject a therapeutically effective amount of a composition comprising one or more natural products selected from the group consisting of withaferin A, sulforaphane, berteroin, genipin, berberine, resveratrol, emodin, piperine, spermidine, beta-hydroxybutyric acid, silybin, forskolin, indole-3-carbinol and cannabidiol.

[0018] Optionally, the method can further comprise dietary intervention, such as the inclusion of omega-3 fatty acids in the diet, or the addition of omega-3 fatty acids as a supplement.

[0019] Preferably, the method comprises administering to the subject a therapeutically effective amount of a composition comprising two or more compounds or extracts selected from withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), and piperine (derived from *Piper nigrum*).

[0020] Optionally, the method can further comprise dietary intervention, such as the inclusion of omega-3 fatty acids in the diet, or the addition of omega-3 fatty acids as a supplement.

[0021] In another example, the present disclosure resides broadly in a method of treating and/or preventing a condition associated with sterile inflammation, the method comprising administering to the subject a therapeutically effective amount of a composition comprising one or more natural products selected from the group consisting of withaferin A, sulforaphane, berteroin, genipin, berberine, resveratrol, emodin, piperine, spermidine, beta-hydroxybutyric acid, silybin, forskolin, indole-3-carbinol and cannabidiol.

[0022] Optionally, the method can further comprise dietary intervention, such as the inclusion of omega-3 fatty acids in the diet, or the addition of omega-3 fatty acids as a supplement.

[0023] Preferably, the method comprises administering to the subject a therapeutically effective amount of a composition comprising two or more compounds or extracts selected from withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), and piperine (derived from *Piper nigrum*).

[0024] Optionally, the method can further comprise dietary intervention, such as the inclusion of omega-3 fatty acids in the diet, or the addition of omega-3 fatty acids as a supplement.

[0025] In another example, the present disclosure resides broadly in the use of one or more natural products selected from the group consisting of withaferin A, sulforaphane, berteroin, genipin, berberine, resveratrol, emodin, piperine, spermidine, beta-hydroxybutyric acid, silybin, forskolin, indole-3-carbinol and cannabidiol, in the manufacture of a medicament for protecting a subject from sterile inflammation.

[0026] In another example, the present disclosure resides broadly in the use of two or more compounds or extracts selected from withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), and piperine (derived from *Piper nigrum*), in the manufacture of a medicament for protecting a subject from sterile inflammation.

[0027] In another example, the present disclosure resides broadly in the use of one or more natural products selected from the group consisting of withaferin A, sulforaphane, berteroin, genipin, berberine, resveratrol, emodin, piperine, spermidine, beta-hydroxybutyric acid, silybin, forskolin, indole-3-carbinol and cannabidiol, in the manufacture of a medicament for treating and/or preventing a condition associated with sterile inflammation.

[0028] In another example, the present disclosure resides broadly in the use of two or more compounds or extracts selected from withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), and piperine (derived from *Piper nigrum*), in the manufacture of a medicament for treating and/or preventing a condition associated with sterile inflammation.

[0029] In another example, the present disclosure resides broadly in the use of one or more natural products selected from the group consisting of withaferin A, sulforaphane, berteroin, genipin, berberine, resveratrol, emodin, piperine, spermidine, beta-hydroxybutyric acid, silybin, forskolin, indole-3-carbinol and cannabidiol, for protecting a subject from sterile inflammation.

[0030] Additionally, dietary intervention, such as the inclusion of omega-3 fatty acids in the diet or provided as a supplement can be used to provide improved protection from sterile inflammation.

[0031] In another example, the present disclosure resides broadly in the use of two or more compounds or extracts selected from withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), and piperine (derived from *Piper nigrum*), for protecting a subject from sterile inflammation.

[0032] Optionally, dietary intervention, such as the inclusion of omega-3 fatty acids in the diet, alone or in combination with compounds or extracts selected from withaferin A (derived from Withania somnifera), curcumin (derived from Curcuma longa), and piperine (derived from Piper nigrum) can be used to provide improved protection from sterile inflammation.

[0033] In another example, the present disclosure resides broadly in the use of one or more natural products selected from the group consisting of withaferin A, sulforaphane, berteroin, genipin, berberine, resveratrol, emodin, piperine, spermidine, beta-hydroxybutyric acid, silybin, forskolin, indole-3-carbinol and cannabidiol, for treating and/or preventing a condition associated with sterile inflammation.

[0034] Additionally, dietary intervention, such as the inclusion of omega-3 fatty acids in the diet, can also be used to provide improved outcomes in treating and/or preventing a condition associated with sterile inflammation.

[0035] In another example, the present disclosure resides broadly in the use of two or more compounds or extracts selected from withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), and piperine (derived from *Piper nigrum*), for treating and/or preventing a condition associated with sterile inflammation.

[0036] Optionally, dietary intervention, such as the inclusion of omega-3 fatty acids in the diet, can also be used with the two or more compounds or extracts to provide improved outcomes for treating and/or preventing a condition associated with sterile inflammation.

[0037] Compositions of the present disclosure can further comprise pharmaceutically acceptable carriers, diluents and/or excipients. Pharmaceutically acceptable carriers, diluents and excipients which can be used in the compositions of the present disclosure will be known to those of skill in the art. The British Pharmacopoeia (BP) and the United States Pharmacopeia and National Formulary (USP-NF) contain details of suitable carriers, diluents and excipients, as does Sweetman S (Ed.), 'Martindale: The complete drug reference.' London: Pharmaceutical Press, 37th Ed., (2011), and Rowe RC, Sheskey PJ, Quinn ME (Ed.), 'Handbook of Pharmaceutical Excipients', 6th Ed., London: Pharmaceutical Press (2009), the contents of which are incorporated herein by cross reference.

[0038] The compositions of the present disclosure can be formulated for oral administration. The compositions can thus be in the form of a powder, a liquid solution, a suspension, a dispersion, an emulsion, a tablet, a pill or a capsule.

[0039] In a particular example, the compositions of the present disclosure are formulated as a lipid complex. The lipid complex can comprise a single lipid, or a combination of two or more

lipids.

[0040] In an alternative example, compositions of the present disclosure can be formulated into a nanoparticle delivery system.

[0041] In a further alternative example, compositions of the present disclosure can be formulated into a cyclodextrin-based carrier. This exampleis advantageous, due to the characteristics of cyclodextrins. Specifically, as cyclodextrins are hydrophobic on their interior, and hydrophilic on their exterior, they can form complexes with hydrophobic compounds and extracts, and therefore act to enhance the solubility and thus bioavailability of natural compounds and plant extracts. Cyclodextrins can also enhance permeability of compounds and extracts through mucosal tissues. One or more of alpha-, beta- and gamma-cyclodextrins can be used as carriers in delivery systems in the present present disclosure.

[0042] In a further alternative example, compositions of the present disclosure can be incorporated into a liposome structure consisting of a spherical vesicle having at least one lipid bilayer. The liposome can be used as a vehicle for administration of compositions of the present disclosure. The liposomes can comprise phospholipids, in particular phosphatidylcholine, but can comprise other lipids that are compatible with formation of lipid bilayer structures and are useful for drug delivery.

[0043] Any of the features described herein can be combined in any combination with any one or more of the other features described herein within the scope of the present disclosure.

[0044] The reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

BRIEF DESCRIPTION OF DRAWINGS

[0045] Preferred features, embodiments and variations of the invention may be discerned from the following Detailed Description which provides sufficient information for those skilled in the art to perform the invention. The Detailed Description is not to be regarded as limiting the scope of the preceding Summary of the Invention in any way. The Detailed Description will make reference to a number of drawings as follows:

[0046] Figure 1 illustrates validation of the use of the THP-1 cell line to study inflammation. Figure 1A is a standard curve generated using the BioLegend human IL-1β ELISA kit. Figure 1B is a graph of the results of the THP-1 inflammasome assay.

[0047] Figure 2 is a graph of the results from a natural compound screen for inhibitors of

CLAIMS

1. A composition comprising one or more natural products selected from the group consisting of compounds that can be isolated from plants of the genera *Withania* present within the concentration range of 3-350 nM; one or more omega-3 fatty acids present within the concentration range of 1340 nM – 85 µM, and:

(i) an extract of turmeric (from plants of *Curcuma longa*) present within the concentration range of 99 nM – 21 µM; or

(ii) an extract of pepper (from plants of *Piper nigrum*) present within the concentration range of 135 nM – 410 µM; or

(iii) an extract of turmeric (from plants of *Curcuma longa*) present within the concentration range of 99 nM – 21 µM, and an extract of pepper (from plants of *Piper nigrum*) present within the concentration range of 135 nM – 410 µM;

wherein the combination of one or more omega-3 fatty acids, and extracts from *Withania*, turmeric and/or pepper is a synergistic combination,

wherein the synergistic combination is within a low dose range of up to Fa 0.65.

2. The composition of claim 1, wherein the one or more natural products selected from the group consisting of compounds that can be isolated from plants of the genera *Withania*, comprises an extract of ashwagandha (from plants of *Withania somnifera*).

3. The composition of claim 1, wherein the one or more natural products selected from the group consisting of compounds that can be isolated from plants of the genera *Withania*, comprises withaferin A.

4. The composition of any one of claims 1 to 3, wherein the one or more omega-3 fatty acids are selected from the group consisting of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

5. The composition of claim 4, wherein the composition comprises docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

6. The composition of claim 4, wherein the composition comprises DHA.

7. The composition of claim 4, wherein the composition comprises EPA.

8. The composition of any one of claims 1 to 7, further comprising one or more pharmaceutically acceptable carriers, diluents and/or excipients.

9. The composition of any one of claims 1 to 8, wherein the composition is formulated for

oral administration.

10. The composition of any one of claims 1 to 9, wherein the composition is in the form of a powder, a liquid solution, a liposomal solution, a suspension, a dispersion, an emulsion, a tablet, a pill or a capsule.

11. A composition of any one of claims 1 to 10, for use in protecting a subject from sterile inflammation.

12. A composition of any one of claims 1 to 10, for use in treating and/or preventing a condition associated with sterile inflammation.

13. Use of withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), piperine (derived from *Piper nigrum*), and one or more omega-3 fatty acids in the manufacture of a medicament for protecting a subject from sterile inflammation.

14. The use of claim 13, wherein the medicament comprises a synergistic combination of withaferin A, piperine, curcumin and the one or more omega-3 fatty acids, wherein the synergistic combination is within a low dose range of up to Fa 0.4.

15. Use of withaferin A (derived from *Withania somnifera*), curcumin (derived from *Curcuma longa*), piperine (derived from *Piper nigrum*), and one or more omega-3 fatty acids in the manufacture of a medicament for treating and/or preventing a condition associated with sterile inflammation.

16. The use of claim 15, wherein the medicament comprises a synergistic combination of withaferin A, piperine, curcumin, and the one or more omega-3 fatty acids, wherein the synergistic combination is within a low dose range of up to Fa 0.4.

17. Use of a composition of any one of claims 1 to 10, in the manufacture of a medicament for protecting a subject from sterile inflammation.

18. Use of a composition of any one of claims 1 to 10, in the manufacture of a medicament for treating and/or preventing a condition associated with sterile inflammation.