diabetes, treating inflammation and its associated diseases, and/or lowering blood cholesterol.

Summary

[0006] The present disclosure has identified a composition comprising *Pinus pinaster* stem bark extract, papain, and *Aloe vera* extract that exerts a number of health benefits, for example, the ability to improve organ function, reduce inflammation, and regulate blood sugar levels.

[0007] Accordingly, the present disclosure provides a composition comprising *Pinus pinaster* stem bark extract, papain, and *Aloe vera* extract.

[0007a] In one aspect, the present disclosure provides a composition comprising *Pinus pinaster* stem bark extract, papain, *Aloe vera* extract, and an acid, wherein the *Pinus pinaster* stem bark extract is present at a concentration of from 2 mg/mL to 10 mg/mL, the papain is present at a concentration of from 1 mg/mL to 5 mg/mL, and the *Aloe vera* extract is present at a concentration of from 0.5 mg/mL to 4 mg/mL, and wherein the composition has a pH of between 3.2 and 4.2.

[0008] The present disclosure provides a composition comprising a therapeutically effective amount of *Pinus pinaster* stem bark extract, papain, and *Aloe vera* extract.

[0009] The present disclosure provides an aqueous composition comprising about 2.6 mg/mL *Pinus pinaster* stem bark extract, about 2.4 mg/mL papain, and about 1.75 mg/mL *Aloe vera* extract.

[0009a] In another aspect, the present disclosure provides an aqueous composition comprising 2.6 mg/mL *Pinus pinaster* stem bark extract, 2.4 mg/mL papain, and 1.75 mg/mL *Aloe vera* extract, and 2 mg/mL glacial acetic acid.

[0010] The following options may be used in conjunction with the aspects as defined above either individually or in any suitable combination.

[0011] The *Aloe vera* extract may be *Aloe vera* leaf extract.

[0012] The therapeutically effective amount of *Pinus pinaster* stem bark extract may correspond to a daily adult human dosage of from about 60 mg to about 1500 mg *Pinus pinaster* stem bark extract; the therapeutically effective amount of papain may correspond to a daily adult human dosage of from about 30 mg to about 1200 mg papain; and the therapeutically effective amount of *Aloe vera* extract may correspond to a daily adult human dosage of from about 15 mg to about 600 mg *Aloe vera* extract.

[0013] In one embodiment, the therapeutically effective amount of *Pinus pinaster* stem bark extract corresponds to a daily adult human dosage of about 260 mg; the therapeutically effective amount of papain corresponds to a daily adult human dosage of about 240 mg; and the therapeutically effective amount of *Aloe vera* extract corresponds to a daily adult human dosage of about 175 mg.

[0014] The composition may further comprise an acid. The acid may be acetic acid. The acid may be present in a concentration effective to adjust the pH of the composition to between about

pinaster stem bark extract : dry *Aloe vera* inner leaf juice : honey of 2.40 : 2.60 : 1.75 : 100 by weight.

[0038] In another embodiment, there is provided an aqueous composition comprising papain, *Pinus pinaster* stem bark extract, *Aloe vera* inner leaf juice, and glacial acetic acid in a ratio of papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice : glacial acetic acid of 2.40 : 2.60 : 1.75 : 2.00 by weight.

[0039] In another embodiment, there is provided an aqueous composition comprising papain, *Pinus pinaster* stem bark extract, *Aloe vera* inner leaf juice, honey, and glacial acetic acid in a ratio of papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice : honey : glacial acetic acid of 2.40 : 2.60 : 1.75 : 100 : 2.00 by weight.

[0040] In yet another embodiment, there is provided an aqueous composition comprising papain, *Pinus pinaster* stem bark extract, *Aloe vera* inner leaf juice, honey, glacial acetic acid, and sodium chloride in a ratio of papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice : honey : glacial acetic acid : sodium chloride of 2.40 : 2.60 : 1.75 : 100 : 2.00 : 3.00 by weight.

[0040a] In another aspect, the present disclosure provides an aqueous composition comprising papain, dry *Pinus pinaster* stem bark extract, dry *Aloe vera* inner leaf juice, honey, glacial acetic acid, and sodium chloride in a ratio of papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice : honey : glacial acetic acid : sodium chloride of 2.40 : 2.60 : 1.75 : 100 : 2.00 : 3.00 by weight.

[0041] There is provided an aqueous composition comprising papain, dry *Pinus pinaster* stem bark extract, dry *Aloe vera* inner leaf juice, honey, glacial acetic acid, sodium chloride, potassium sorbate, sodium benzoate, wildberry flavour UA71225 and anthocyanin extract in a ratio of papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice : honey : glacial acetic acid : sodium chloride : potassium sorbate : sodium benzoate : wildberry flavour UA71225 : anthocyanin extract of 2.40 : 2.60 : 1.75 : 100 : 2.00 : 3.00 : 0.40 : 0.40 : 10.00 : 0.80 by weight.

[0041a] In another aspect, the present disclosure provides an aqueous composition comprising papain, *Pinus pinaster* stem bark extract, *Aloe vera* inner leaf juice, honey, glacial acetic acid, sodium chloride, potassium sorbate, sodium benzoate, wildberry flavour UA71225 and anthocyanin extract in a ratio of papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera*

inner leaf juice : honey : glacial acetic acid : sodium chloride : potassium sorbate : sodium benzoate : wildberry flavour UA71225 : anthocyanin extract of 2.40 : 2.60 : 1.75 : 100 : 2.00 : 3.00 : 0.40 : 0.40 : 10.00 : 0.80 by weight.

[0042] The present disclosure provides a method of treating or preventing elevated blood glucose, comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0042a] There is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for treating or preventing elevated blood glucose in a subject.

[0043] The present disclosure provides a method of preventing or delaying the onset of type 2 diabetes mellitus (T2DM), comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0043a] In an aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for preventing or delaying the onset of type 2 diabetes mellitus (T2DM) in a subject.

[0044] The present disclosure provides a method of treating or preventing pre-diabetes, comprising administering to a subject in need thereof an effective amount of a

composition as defined above.

[0044a] In another aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament treating or preventing pre-diabetes in a subject.

[0045] The present disclosure provides a method of reducing inflammation, comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0045a] In another aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for reducing inflammation in a subject.

[0046] The present disclosure provides a method of decreasing cytokine-induced inflammation comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0046a] In another aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament decreasing cytokine-induced inflammation in a subject.

[0047] The present disclosure provides a method of decreasing an oxidative stress response comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0047a] There is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for decreasing an oxidative stress response in a subject.

[0048] The present disclosure provides a method of treating or preventing a disease characterised by elevated levels of cytokine-induced inflammation, comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0048a] In another aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for treating or preventing a disease characterised by elevated levels of cytokine-induced inflammation in a subject, wherein the disease is selected from atherosclerosis, liver inflammation associated with type 2 diabetes and obesity, endometriosis, or osteoarthritis.

[0049] The present disclosure provides a method of treating or preventing a disease characterised by elevated levels of oxidative stress, comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0049a] In another aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for treating or preventing a disease characterised by elevated levels of oxidative stress in a subject, wherein the disease is selected from atherosclerosis, liver inflammation associated with type 2 diabetes and obesity, endometriosis, or osteoarthritis.

[0050] In one embodiment, the disease is atherosclerosis, liver inflammation associated with type 2 diabetes and obesity, endometriosis, or osteoarthritis.

[0051] The present disclosure provides a method of reducing one or more side effects of a diabetes medication selected from the group consisting of metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin therapy, the method comprising administering to a subject in need thereof an effective amount of a composition as defined above. The side effect may be abdominal or stomach discomfort, decreased appetite, or diarrhoea.

[0051a] In another aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for reducing one or more side effects of a diabetes medication selected from the group consisting of metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin therapy in a subject.

[0052] The present disclosure provides a method of treating or preventing a dysfunction associated with excess blood glucose, comprising administering to a subject in need

thereof an effective amount of a composition as defined above. The dysfunction may be selected from the group consisting of: increased thirst and hunger, frequent urination, fatigue/lethargy, blurry vision, sleepiness, and muscle weakness.

[0052a] In another aspect, there is provided the use of an effective amount of a composition as defined above in the manufacture of a medicament for treating or preventing a dysfunction associated with excess blood glucose in a subject.

[0053] In one embodiment, the composition is administered in combination with metformin or another blood glucose lowering medication.

[0054] The present disclosure provides a method of improving organ function comprising administering to a subject in need thereof an effective amount of a composition as defined above.

[0054a] There is provided a use of an effective amount of a composition as defined above in the manufacture of a medicament for improving organ function in a subject.

[0055] The present disclosure provides a method of lowering blood cholesterol, comprising administering to a subject in need thereof an effective amount of a composition as defined above. The blood cholesterol may be selected from the group consisting of: low density lipoproteins (LDL), high density lipoproteins (HDL), trigylcerides and total cholesterol. In one embodiment, the present disclosure provides a method of lowering low density lipoprotein (LDL) blood cholesterol levels, comprising administering to a subject in need thereof an effective amount of a composition as defined above. In another embodiment, the present disclosure provides a method of increasing high density lipoprotein (HDL) blood cholesterol levels, comprising administering to a subject in need thereof an effective amount of a composition as defined above. In yet another embodiment, the present disclosure provides a method of decreasing the ratio of Total Cholesterol to HDL, comprising administering to a subject in need thereof an effective amount of a composition as defined above. In yet another embodiment, the present disclosure provides a method of decreasing blood triglyceride levels, comprising administering to a subject in need thereof an effective amount of a composition as defined above.

as defined above for the manufacture of a medicament for increasing general wellbeing, e.g., increasing energy levels, improving vitality, improving sleep, improving breathing ability, improving levels of physical activity, improving mental functioning, and/or improving physical functioning in a subject.

[0078a] In another aspect, there is provided a method of manufacturing the aqueous composition as defined above, said method comprising: combining *Pinus pinaster* stem bark extract, papain, and *Aloe vera* extract in water.

Brief Description of the Drawings

[0079] Embodiments of the present invention will now be described, by way of example only with reference to the accompanying figures wherein:

[0080] **Figure 1** shows that a composition according to Example 1 decreases inflammatory markers (a) TNF-alpha-induced VCAM-1, (b) TNF-alpha-induced ICAM-1 and (c) TNF-alpha-induced ELAM in human coronary artery endothelial cells. HCAECs were exposed to the indicated amounts (μL/mL) of the composition of Example 1 for 3 hours prior to exposure to TNF-alpha.

[0081] **Figure 2** shows that a composition according to Example 1 decreases protein levels of (a) TNF-alpha-induced VCAM-1 and (b) TNF-alpha-induced ICAM-1 in human coronary artery endothelial cells. HCAECs were exposed to the indicated amounts (μL/mL) of the composition of Example 1 for 3 hours prior to exposure to TNF-alpha.

[0082] **Figure 3** shows that a composition according to Example 1 decreases activation of the key mediator of inflammation, NFkB. HCAECs were exposed to the indicated amounts (μL/mL) of the composition of Example 1 prior to exposure to TNF-alpha.

[0083] **Figure 4** shows that a composition according to Example 1 decreases cytokine-induced ROS levels in TNF-alpha-induced HCAECs. HCAECs were exposed to the indicated amounts (μL/mL) of the composition of Example 1 for 3 hours prior to exposure to TNF-alpha.

[0084] **Figure 5** shows that a composition according to Example 1 decreases (a) NOX-4 and increases (b) SOD-1 levels in TNF-alpha-induced HCAECs. HCAECs were exposed to the indicated amounts (μL/mL) of the composition of Example 1 prior to exposure to TNF-alpha.

[0085] **Figure 6** shows that a composition according to Example 1 ingested by athletes pre-training decreases CRP levels in their blood post-training (dark grey = runners, light grey = cyclists).

[0086] **Figure 7** shows that a composition according to Example 1 blocks VCAM-1 levels from

CLAIMS:

1. A composition comprising *Pinus pinaster* stem bark extract, papain, *Aloe vera* extract, and an acid, wherein

   the *Pinus pinaster* stem bark extract is present at a concentration of from 2 mg/mL to 10 mg/mL,

   the papain is present at a concentration of from 1 mg/mL to 5 mg/mL, and

   the *Aloe vera* extract is present at a concentration of from 0.5 mg/mL to 4 mg/mL, and

   wherein the composition has a pH of between 3.2 and 4.2.

2. The composition according to claim 1, wherein the *Aloe vera* extract is *Aloe vera* leaf extract.

3. The composition according to claim 1 or claim 2, wherein the acid is acetic acid.

4. The composition according to any one of claims 1 to 3, wherein the composition further comprises honey.

5. The composition according to any one of claims 1 to 4, wherein the composition comprises one or more additives selected from the group consisting of: a preservative, a flavouring agent, a salt, and a pigment.

6. The composition according to any one of claims 1 to 5, wherein the composition comprises a salt, and wherein the salt is sodium chloride.

7. The composition according to any one of claims 1 to 6, further comprising an additional component selected from the group consisting of: an omega-3 fatty acid, a phytonutrient, a source of protein, an amino acid, an antioxidant, a vitamin, a mineral, a plant extract, and mixtures thereof.

8. The composition according to any one of claims 1 to 7, wherein the composition is synergistic.

9. The composition according to any one of claims 1 to 8, wherein the composition is adapted for oral administration.

10. The composition according to claim 9, wherein the composition is in a form selected from the group consisting of: a tablet, a capsule, a chewable tablet, a soft gel capsule, a sachet, a powder, granules, a liquid, a syrup, a liquid suspension, an emulsion, a solution, and combinations thereof.

11. The composition according to any one of claims 1 to 10, wherein the composition is an aqueous composition.

12. The composition according to any one of claims 1 to 11, wherein the composition has a pH of 3.7.

13. The composition according to any one of claims 1 to 12, wherein the *Pinus pinaster* stem bark extract is present at a concentration of 2.6 mg/mL.

14. The composition according to any one of claims 1 to 13, wherein the papain is present at a concentration of 2.4 mg/mL.

15. The composition according to any one of claims 1 to 14, wherein the *Aloe vera* extract is present at a concentration of 1.75 mg/mL.

16. The composition according to any one of claims 1 to 15, wherein the composition comprises glacial acetic acid at a concentration of from 1 mg/mL to 8 mg/mL.

17. The composition according to claim 16, wherein the glacial acetic acid is present at a concentration of 2 mg/mL.

18. The composition according to any one of claims 1 to 17, wherein the composition further comprises honey at a concentration of from 50 mg/mL to 200 mg/mL.

19. The composition according to claim 18, wherein the honey is present at a concentration of 100 mg/mL.

20. An aqueous composition comprising 2.6 mg/mL *Pinus pinaster* stem bark extract, 2.4 mg/mL papain, 1.75 mg/mL *Aloe vera* extract, and 2 mg/mL glacial acetic acid.

21. The composition according to claim 20, further comprising 100 mg/mL honey.

22. An aqueous composition comprising:
2.40 mg/mL papain;
2.60 mg/mL *Pinus pinaster* stem bark extract;
1.75 mg/mL *Aloe vera* inner leaf juice;
100.00 mg/mL honey;
2.00 mg/mL glacial acetic acid;
3.00 mg/mL sodium chloride;
400 µg/mL potassium sorbate;
400 µg/mL sodium benzoate;
10.00 mg/mL wildberry flavour UA71225; and
800 µg/mL anthocyanin extract.

23. An aqueous composition comprising papain, *Pinus pinaster* stem bark extract, *Aloe vera* inner leaf juice, honey, glacial acetic acid, sodium chloride, potassium sorbate, sodium benzoate, wildberry flavour UA71225 and anthocyanin extract
in a ratio of
papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice : honey : glacial acetic acid : sodium chloride : potassium sorbate : sodium benzoate : wildberry flavour UA71225 : anthocyanin extract
of 2.40 : 2.60 : 1.75 : 100 : 2.00 : 3.00 : 0.40 : 0.40 : 10.00 : 0.80 by weight.

24. An aqueous composition comprising papain, dry *Pinus pinaster* stem bark extract, dry *Aloe vera* inner leaf juice, honey, glacial acetic acid, and sodium chloride
in a ratio of
papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice : honey : glacial acetic acid : sodium chloride
of 2.40 : 2.60 : 1.75 : 100 : 2.00 : 3.00 by weight.

25. An aqueous composition comprising papain, *Pinus pinaster* stem bark extract, and *Aloe vera* inner leaf juice in a ratio of
papain : dry *Pinus pinaster* stem bark extract : dry *Aloe vera* inner leaf juice
of 2.40 : 2.60 : 1.75 by weight.

26. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for preventing or delaying the onset of type 2 diabetes mellitus (T2DM) in a subject.

27. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for treating or preventing pre-diabetes in a subject.

28. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for reducing inflammation in a subject.

29. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for decreasing cytokine-induced inflammation in a subject.

30. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for treating or preventing a disease characterised by elevated levels of cytokine-induced inflammation in a subject, wherein the disease is selected from atherosclerosis, liver inflammation associated with type 2 diabetes and obesity, endometriosis, or osteoarthritis.

31. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for treating or preventing a disease characterised by elevated levels of oxidative stress in a subject, wherein the disease is selected from atherosclerosis, liver inflammation associated with type 2 diabetes and obesity, endometriosis, or osteoarthritis.

32. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for reducing one or more side effects of a diabetes medication selected from the group consisting of metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4

inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin therapy in a subject.

33. The use of claim 32, wherein the side effect is abdominal or stomach discomfort, decreased appetite, or diarrhoea.

34. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for treating or preventing a dysfunction associated with excess blood glucose in a subject.

35. The use of claim 34, wherein the dysfunction is selected from the group consisting of: increased thirst and hunger, frequent urination, fatigue/lethargy, blurry vision, and muscle weakness.

36. The use of any one of claims 26 to 35, wherein the composition is to be administered in combination with metformin or another blood glucose lowering medication.

37. Use of an effective amount of a composition according to any one of claims 1 to 25 in the manufacture of a medicament for treating an autoimmune disease in a subject.

38. The use of claim 37, wherein the autoimmune disease is selected from the group consisting of: lupus, arthritis, psoriasis, and type I diabetes.

39. The use according to any one of claims 26 to 38, wherein the effective amount of the composition corresponds to:
a daily adult human dosage of from about 60 mg to about 1500 mg *Pinus pinaster* stem bark extract;
a daily adult human dosage of from about 30 mg to about 1200 mg papain; and
a daily adult human dosage of from about 15 mg to about 600 mg *Aloe vera* extract.

40. The use according to any one of claims 26 to 39, wherein the effective amount of the composition corresponds to:
a daily adult human dosage of about 260 mg *Pinus pinaster* stem bark extract;
a daily adult human dosage of about 240 mg papain; and
a daily adult human dosage of about 175 mg *Aloe vera* extract.

41. The use according to claim 39 or claim 40, wherein the daily adult human dosage of *Pinus pinaster* stem bark extract, papain and *Aloe vera* extract is to be provided to the subject in a single dose.

42. The use according to claim 39 or claim 40, wherein the daily adult human dosage of *Pinus pinaster* stem bark extract, papain and *Aloe vera* extract is to be provided to the subject in multiple doses.

43. The use of any one of claims 26 to 42, wherein the subject is selected from the group consisting of the elderly, those with a medical condition of pre-diabetes or at risk of developing pre-diabetes, and combinations thereof.

44. The use of claim 43, wherein the subject is taking metformin or another blood glucose lowering medication.

45. A method of manufacturing the aqueous composition of any one of claims 1 to 25, said method comprising:
combining *Pinus pinaster* stem bark extract, papain, and *Aloe vera* extract in water.

46. The method of claim 45, wherein the method further comprises:
adding an acid.

47. The method of claim 46, wherein the acid is glacial acetic acid.

48. The method of any one of claims 45 to 47, further comprising:
adding honey.