Summary

The present disclosure provides polymer-flavonoid conjugates, useful in the therapeutic and/or prophylactic treatment of a joint condition in a subject. The present disclosure further provides a process for forming said polymer-flavonoid conjugates.

According to the present disclosure, there is provided the use of a polymer-flavonoid conjugate, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a joint condition in a subject.

According to a first aspect of the present disclosure, there is provided the use of a polymer-flavonoid conjugate, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a joint condition in a subject, wherein the polymer of said polymer-flavonoid conjugate is conjugated to one or more flavonoids at the C6 and/or C8 position of the A ring or the C2 and/or C6 position of the B ring of said flavonoid(s), and

wherein the joint condition is selected from the group consisting of osteoarthritis, rheumatoid arthritis, gouty arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis.

In the present disclosure, there is provided a polymer-flavonoid conjugate, or a pharmaceutically acceptable salt thereof, for use in the therapeutic and/or prophylactic treatment of a joint condition in a subject.

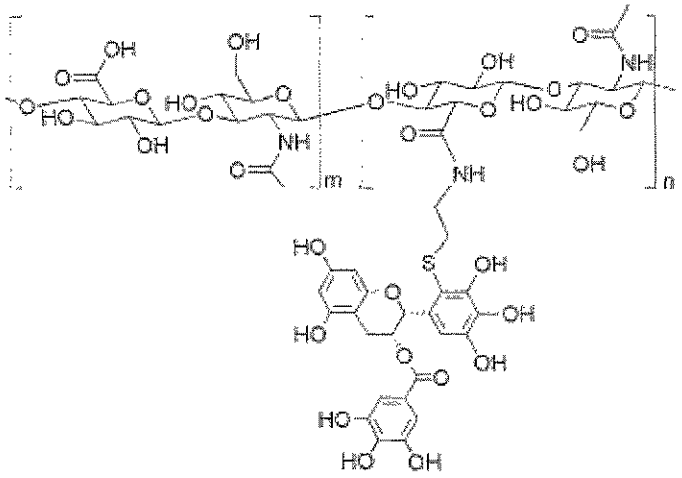
In a second aspect of the present disclosure, there is provided the use of a polymer-flavonoid conjugate, or a

pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a joint condition in a subject, wherein the polymer of said polymer-flavonoid conjugate is conjugated to one or more flavonoids at the C6 and/or C8 position of the A ring or the C2 and/or C6 position of the B ring of said flavonoid(s),

wherein the joint condition is selected from the group consisting of osteoarthritis, rheumatoid arthritis, gouty arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis, and

wherein said polymer is a polysaccharide and said flavonoid is epigallocatechin gallate.

In a third aspect of the present disclosure, there is provided the use of a polymer-flavonoid conjugate of Formula 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a joint condition in a subject:



Formula 1;

wherein:

each n is independently an integer from 0 to 50,000 inclusive; and each m is independently an integer from 0 to 50,000 inclusive, wherein n is not 0.

In the present disclosure, there is provided a method of treating or preventing a joint condition comprising administering a therapeutically effective amount of a polymer-flavonoid conjugate to a subject.

Advantageously, the disclosed polymer-flavonoid conjugates of the first to third aspects may be used in the treatment of osteoarthritis. The disclosed polymer-flavonoid conjugates of the first aspect may advantageously improve joint function and reduce pain.

Further advantageously, the disclosed polymer-flavonoid conjugates of the first to third aspects may restore a cartilage defect thereby repairing the cartilage.

Advantageously, the use of the disclosed polymer-flavonoid conjugates of the first to third aspects may

Claims

1. Use of a polymer-flavonoid conjugate, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a joint condition in a subject, wherein the polymer of said polymer-flavonoid conjugate is conjugated to one or more flavonoids at the C6 and/or C8 position of the A ring or the C2 and/or C6 position of the B ring of said flavonoid(s), and
wherein the joint condition is selected from the group consisting of osteoarthritis, rheumatoid arthritis, gouty arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis.

2. The use according to claim 1, wherein said therapeutic and/or prophylactic treatment of the joint condition results in cartilage repair.

3. The use according to claim 1 or 2, wherein one or more flavonoids are conjugated to said polymer.

4. The use according to any one of claims 1 to 3, wherein said polymer is conjugated to said one or more flavonoids via a linker.

5. The use according to any one of claims 1 to 4, wherein said one or more flavonoids is a monomeric flavonoid or a dimeric flavonoid,

preferably wherein the flavonoid is selected from the group consisting of flavones, isoflavones, flavans, proanthocyanidins, anthocyanidins, (-)-epicatechin, (+)-epicatechin, (-)-catechin, (+)-catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, Fisetinidol, Gallocatechin, Gallocatechin gallate, Mesquitol and Robinetinidol, ellagitannin, gallotannin, oolongtheanin, phlorotannin, tannin, theacitrin, theadibenzotropolone, theaflavin, theanaphthoquinone, thearubigins, theasinensin and mixtures thereof.

6. The use according to any one of claims 1 to 5, wherein the polymer is conjugated to the flavonoid at the C6 and/or C8 position of the A ring of said flavonoid.

7. The use according to any one of claims 1 to 6, wherein the polymer contains a free aldehyde or a group that can be converted to a free aldehyde in the presence of an acid, the polymer conjugated at the C6 and/or C8 position of the A ring of the flavonoid by attachment of the polymer via reaction of the free aldehyde group with the C6 and/or C8 position of the A ring of said flavonoid.

8. The use according to any one of claims 1 to 5, wherein the polymer is conjugated to the flavonoid at the C2 and/or C6 position of the B ring of said flavonoid,

preferably, wherein the polymer is conjugated to the flavonoid via a thiol linker,

preferably wherein said thiol linker further comprises a moiety bound to the polymer, wherein said moiety is selected from the group consisting of an amide, an amine, an alkyl, an alkenyl, an aryl, an ester, a carbonate, an ether, an amido, an amido ester, a carbamate and an acetal group.

9. The use according to any one of claims 1 to 8, wherein the polymer is selected from the group consisting of polysaccharides, polynucleotides, polypeptides, synthetic polymers and mixtures thereof,

preferably wherein the polysaccharide is selected from the group consisting of hyaluronic acid, dextran, cellulose, amylose, starch, gelatin, alginate, chitosan, carrageenan, cyclodextrin, dextran sulfate, Ficoll, gellan, guar gum, pectin, polysucrose, pullulan, scleroglucan, xanthan and xyloglucan,

preferably wherein the polynucleotide is selected from the group consisting of

aptamers, DNA, small interfering RNA (siRNA), microRNA, peptide nucleic acid (PNA) and small hairpin RNA (shRNA),

preferably wherein the polypeptide is selected from the group consisting of proteins, antibodies, antibody fragments, aptides, peptides and poly(amino acid)s, preferably wherein the synthetic polymer comprises monomers selected from the group consisting of alkenes, ethers, carboxylic acids, imines, amides, amines, anhydrides, carbonates, esters, orthoesters, urethanes,poly(acrylamide),poly(allylamine), polyanhydrides, poly(β-amino ester), poly(butylene succinate), polycaprolactone, polycarbonate, polydioxanone, polyethylenimine, poly(glycerol), polyglycolic acid, poly(3-hydroxypropionic acid), poly(*N*-(2-hydroxypropyl)methacrylamide), polylactic acid, poly(lactic-*co*-glycolic acid), poly(acrylic acid), poly(methacrylic acid), poly(ortho esters), poly(2-oxazoline), poly(sebacic acid), poly(terephthalate-*co*-phosphate), poly(vinyl alcohol), poly(vinylpyrrolidone) and combinations thereof.

10. Use of a polymer-flavonoid conjugate, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a joint condition in a subject, wherein the polymer of said polymer-flavonoid conjugate is conjugated to one or more flavonoids at the C6 and/or C8 position of the A ring or the C2 and/or C6 position of the B ring of said flavonoid(s),

wherein the joint condition is selected from the group consisting of osteoarthritis, rheumatoid arthritis, gouty arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis, and

wherein said polymer is a polysaccharide and said flavonoid is epigallocatechin gallate.

11. The use according to any one of claims 9 or 10, wherein the polysaccharide is conjugated to at least one epigallocatechin gallate.

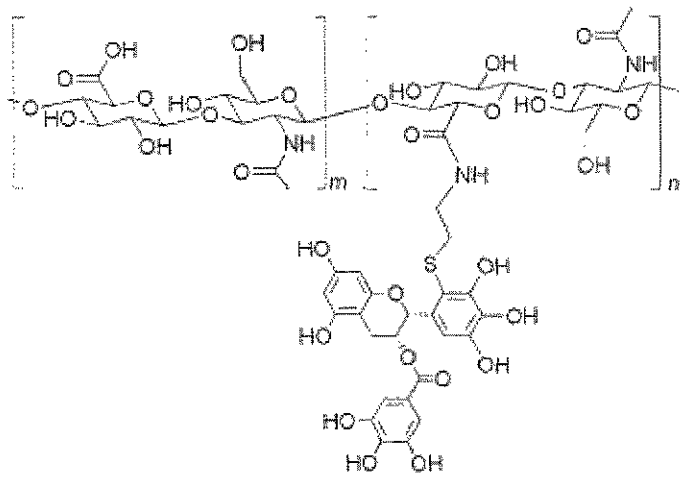
12. The use according to any one of claims 10 or 11, wherein the polysaccharide is conjugated to two epigallocatechin gallate.

13. The use according to any one of claims 10 or 11, wherein the polysaccharide is conjugated to at least one epigallocatechin gallate via a thiol linker.

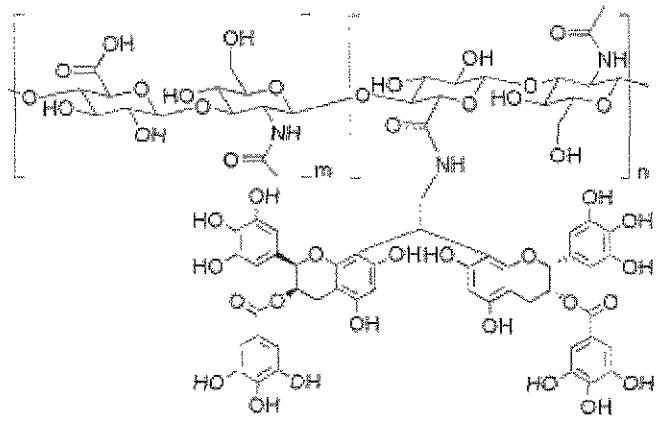
14. The use according to any one of claims 10, 11 or 13, wherein the polysaccharaide is conjugated to at least one epigallocatechin gallate at the C2 and/or C6 ring of the B ring of said epigallocatechin gallate.

15. The use according to any one of claims 10 to 12 wherein the polysaccharide is conjugated to at least one epigallocatechin gallate at the C6 and/or C8 position of the A ring of said epigallocatechin gallate.

16. The use according to any one of claims 1 to 15, wherein the polymer-flavonoid conjugate is of Formula 1 or Formula 2:



Formula 1;

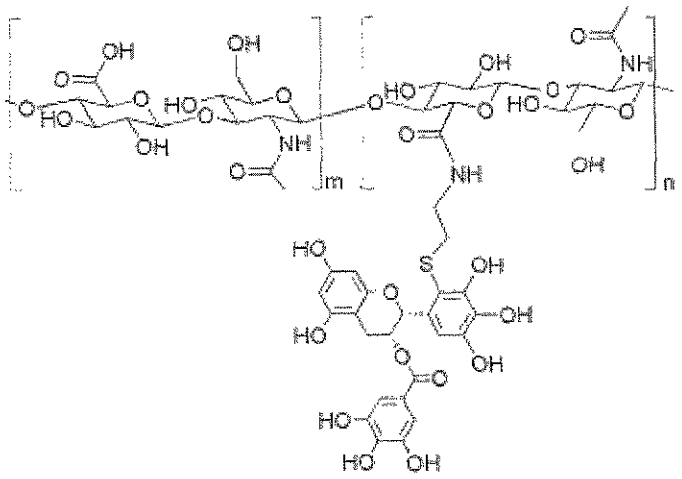


Formula 2;

wherein:

each n is independently an integer from 0 to 50,000 inclusive; and each m is independently an integer from 0 to 50,000 inclusive, wherein n is not 0 .

17. Use of a polymer-flavonoid conjugate of Formula 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a joint condition in a subject:



Formula 1;

wherein:

each n is independently an integer from 0 to 50,000 inclusive; and each m is independently an integer from 0 to 50,000 inclusive, wherein n is not 0.

18. The use according to claim 16 or 17, wherein the polymer-flavonoid conjugate of Formula 1 or Formula 2 has a degree of conjugation from 0.1 to 50%.

19. A process for forming a polymer-flavonoid conjugate comprising the steps of:

(a) linking an amine-containing compound to one or more flavonoids to thereby form a flavonoid(s) bearing a free amine group; and

(b) conjugating the product of (a) with a polymer via nucleophilic addition.

20. The process according to claim 19, wherein step (a) comprises linking an amine-containing compound to two

flavonoids to thereby form an amine-containing-bridged flavonoid dimer, or

wherein step (b) is conducted in the presence of a coupling agent, preferably wherein the coupling agent is selected from the group consisting of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC.HCl), hydrochloride1-ethyl-3-(3-dimethyl dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), carbonyldiimidazole, dimethyl adipimidate, *N*-hydroxysuccinimide, *p*-nitrophenyl chloroformate and 1-(*p*-toluenesulfonyl)imidazole.