conjugates. A complicated purification step is then necessary to obtain the desired conjugates in high yield and purity.

[007] There is therefore a need to find an effective way to modify flavonoids, such as EGCG, with thiol-containing compounds in a highly selective manner.

[008] Furthermore, there is currently also no way to make stable polymer-flavonoid conjugates. There is however a need to create such conjugates in order to improve the poor stability of the flavonoids and make them available in biomedical applications, such as gels.

Summary

[009]According to the disclosure, there is provided a polymer-flavonoid conjugate, wherein said polymer is conjugated to said flavonoid via a thiol linker.

[009a] According to the disclosure, there is provided a polymer-flavonoid conjugate, wherein said polymer is conjugated to said flavonoid via a thiol linker and the polymer is selected from the group consisting of polysaccharides, polynucleotides, synthetic polymers and mixtures thereof.

[009b] According to a first aspect, there is provided a polymer-flavonoid conjugate, wherein said polymer is conjugated specifically to a B ring of said flavonoid via a thiol linker and the polymer is selected from the group consisting of polysaccharides, synthetic polymers and mixtures thereof.

[010]Advantageously, the conjugates link the polymer in a stable way to the flavonoid moiety via a thiol link. It is possible to obtain flavonoid-terminated polymers and flavonoid-grafted polymers with improved bioavailability and bioactivity of the flavonoid.

[011]Further advantageously, the conjugation to biocompatible and biodegradable polymers was achieved which has a potential use in biomedical applications.

[012]According to the disclosure, there is provided a process for forming a polymer-flavonoid conjugate comprising the step of conjugating said flavonoid with said polymer via nucleophilic addition under basic conditions, wherein said polymer has been modified with a free thiol group.

[012a] According to a second aspect, there is provided a process for forming a polymer-flavonoid conjugate as defined herein comprising the step of conjugating said polymer specifically to a B ring of said flavonoid via nucleophilic addition under basic conditions, wherein said polymer has been modified with a free thiol group.

[013]Advantageously, the disclosed process allows for the reaction with very high degrees of conjugation which avoids cumbersome separation processes. The thiol

conjugation can be achieved at specific points of the flavonoid structure using the disclosed process.

[014]According to the disclosure, there is provided a hydrogel comprising a polymer-flavonoid conjugate, wherein said polymer is conjugated to said flavonoid via a thiol linker.

[014a] According to a third aspect, there is provided a hydrogel comprising a polymer-flavonoid conjugate as defined herein.

[015] Advantageously, the hydrogels could be made by the simple crosslinking of the flavonoid moieties of the disclosed conjugates, particularly when autoxidation or enzymatic crosslinking reactions are employed. The obtained hydrogels have a good storage modulus of more than about 200 pascal, often even more than 390 pascal.

[016]According to a fourth aspect, there is therefore provided a process for forming a hydrogel comprising the step of cross-linking a polymer-flavonoid conjugate as defined herein via autoxidation under basic conditions. This is optionally accelerated by adding an enzyme and oxidant.

[017]According to the disclosure, there is provided the use of the hydrogels as defined herein for making biomedical products.

[018]Advantageously, the hydrogels can be used in injectable hydrogel systems which provide an effective and convenient way to administer a variety of bioactive and therapeutic agents for diverse biomedical applications by choosing the flavonoid moiety and the polymer type in the conjugates as needed.

Definitions

[019]Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry

Claims

1. A polymer-flavonoid conjugate, wherein said polymer is conjugated specifically to a B ring of said flavonoid via a thiol linker and the polymer is selected from the group consisting of polysaccharides, synthetic polymers and mixtures thereof.

2. The polymer-flavonoid conjugate according to claim 1, wherein said polysaccharide is selected from the group consisting of hyaluronic acid, alginate, gellan gum, pectin, and xanthan gum.

3. The polymer-flavonoid conjugate according to claim 1, wherein said synthetic polymer comprises carboxylic acid monomers, .

4. The polymer-flavonoid conjugate according to claim 3, wherein said synthetic polymer is selected from the group consisting of polyacrylic acid,

polyglycolic acid, poly(3-hydroxypropionic acid), polylactic acid, poly(lactic-*co*-glycolic acid), poly(methacrylic acid), poly(sebacic acid) and combinations thereof.

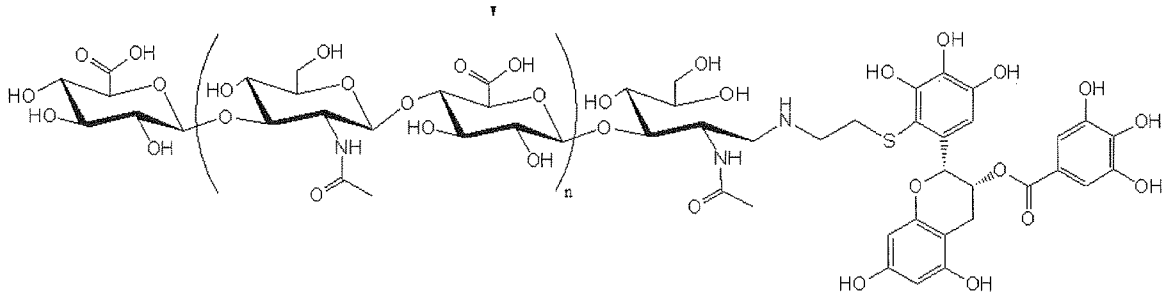
5. The polymer-flavonoid conjugate according to claim 1, wherein said polymer is selected from polyacrylic acid or hyaluronic acid.

6. The polymer-flavonoid conjugate according to claim 6, wherein said flavonoid is selected from the group consisting of epigallocatechin, epigallocatechin gallate, Gallocatechin, Gallocatechin gallate, Robinetinidol, ellagitannin, gallotannin, oolongtheanin, tannin, theacitrin, theasinensin and mixtures thereof.

7. The polymer-flavonoid conjugate according to claim 1, wherein said polymer-flavonoid conjugate is a

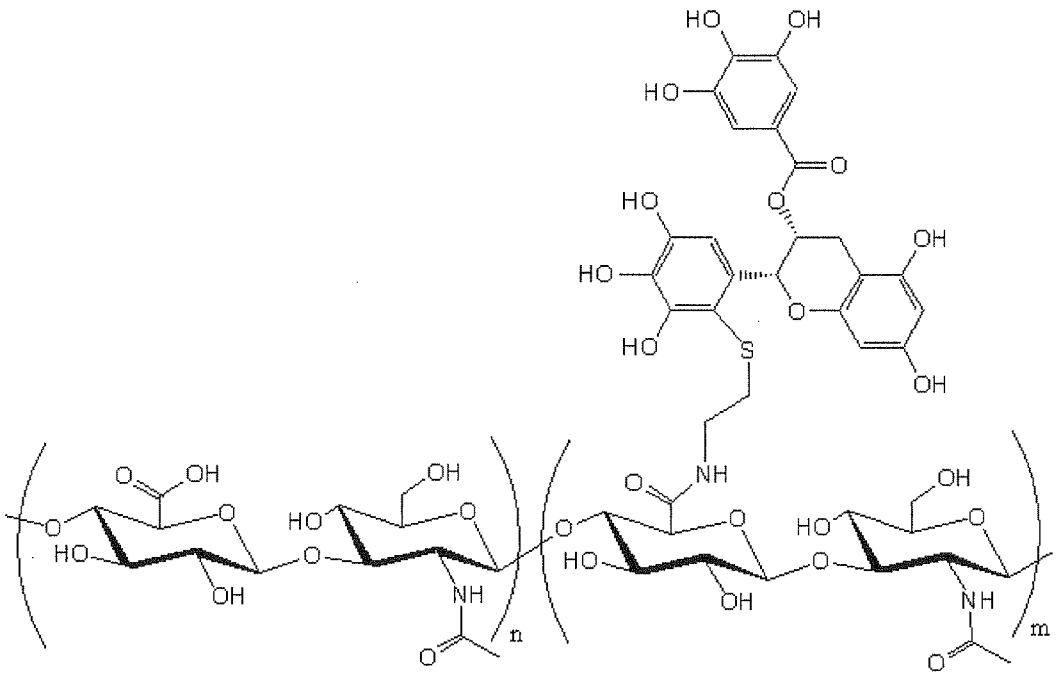
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Hyaluronic acid-EGCG conjugate which is selected from the group consisting of:



(I)

Formula (I); and



(II)

Formula (II)

wherein:

each n is independently an integer from 0 to 15,000 inclusive; and each m is independently an integer from 1 to 15,000 inclusive.

8. The polymer-flavonoid conjugate according to claim 7, wherein said polymer-flavonoid conjugate is of

the Formula (I) or (II) and has a degree of conjugation from 0.01 to 100%.

9. A process for forming a polymer-flavonoid conjugate according to claim 1 comprising the step of conjugating said polymer specifically to a B ring of said flavonoid via nucleophilic addition under basic conditions, wherein said polymer has been modified with a free thiol group.

10. The process according to claim 9, further comprising the steps of:

(a) linking a thiol or disulphide-containing compound to said polymer in the presence of a reducing agent; and

(b) cleaving said disulphide-containing compound at the disulphide bond to thereby form said polymer bearing a terminal thiol group.

11. The process according to claim 10, wherein said reducing agent is selected from the group consisting of sodium cyanoborohydride, sodium borohydride, and sodium triacetoxyborohydride.

12. The process according to any one of claims 9 to 11, wherein said conjugating step is undertaken at a reaction time of between 1 to 24 hours.

13. The process according to claim 9, further comprising the step of coupling a thiol or disulphide- containing compound to said polymer in the presence of a coupling agent.

14. The process according to claim 13, wherein said 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.

15. The process according to claim 13 wherein the coupling agent is selected from 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM).

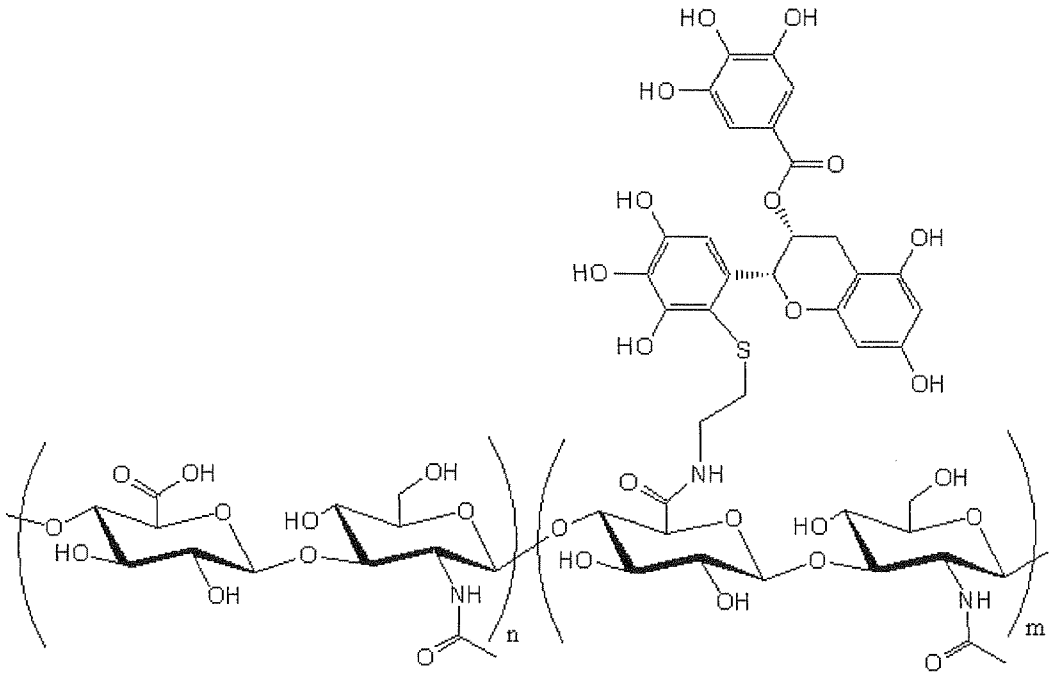
16. The process according to any one of claims 9 to 15, further comprising the step of adding a scavenging agent in the nucleophilic addition.

17. The process according to claim 16, wherein said scavenging agent is selected from the group consisting of sodium pyruvate and superoxide dismutase.

18. The process according to any one of claims 9 to 17, wherein said basic conditions in the nucleophilic addition is in the pH range of about 7.0 to 10.0.

19. A hydrogel comprising a polymer-flavonoid conjugate according to claim 1.

20. The hydrogel according to claim 19, wherein said polymer-flavonoid conjugate is of the Formula (II)



(II)

and has a degree of conjugation from 0.01 to 100 %.

21. A process for forming a hydrogel comprising the step of cross-linking a polymer-flavonoid conjugate according to any of claims 1 to 8 via autoxidation under basic conditions.

22. A process according to claim 21, wherein said cross-linking step further comprises the step of adding an enzyme in the presence of an oxidant.

23. The process according to claim 21, wherein said enzyme is a peroxidase.

24. The process according to claim 23, wherein said peroxidase is selected from the group consisting of horseradish peroxidase, human myeloperoxidase, lactoperoxidase, eosinophil peroxidase, thyroid peroxidase, prostaglandin H synthases, soybean peroxidase, hemin, hematin and microperoxidase-11.

25. The process according to any one of claims 21 to 24, wherein said oxidant is a peroxide.

26. The process according to claim 25, wherein said peroxide is hydrogen peroxide.

27. The process according to any one of claims 21 to 26, wherein said cross-linking step is undertaken at a reaction time of about 2 minutes to 45 hours.

28. The process according to any one of claims 21 to 27, wherein said cross-linking step is undertaken at a temperature selected from the range of about 35°C to 39°C.