

COMPOSITIONS

FIELD OF THE INVENTION

[0001] The present invention relates to cranberry fruit product. In particular, the invention relates to biological, therapeutic effects and non-therapeutic effects of a
5 cranberry fruit product and compositions comprising the cranberry fruit product.

BACKGROUND OF INVENTION

[0002] Urinary tract infections (UTIs) are among the most common infectious diseases, and account for considerable healthcare outlays for society. Microorganisms can reach the urinary tract by a hematogenous or a lymphatic route, but most clinical and
10 experimental evidence shows that ascension of the urethra by microorganisms constitutes the most common route leading to urinary tract infection, in particular by enteric organisms (*Escherichia coli* and other enterobacteria). Women are at greater risk of developing a UTI than are men. Dysbiosis is often defined as an “imbalance” in for example the urinary microbial community that is associated with disease. This imbalance
15 could be due to the gain or loss of community members or changes in relative abundance of microbes.

[0003] Finding new ways of managing those UTIs and the associated dysbiosis is very valuable for the comfort of the patients.

SUMMARY OF THE INVENTION

20 [0004] The authors of the present invention have investigated the biological effects of a cranberry fruit product in Urinary tract infections (UTI) and the impact of these products on the human urinary tract microbiome. The inventors of the present invention have surprisingly observed a significant lower relative abundance of *Gardnerella* in the urinary microbiome of women after 6 months of treatment with the cranberry fruit product of the
25 invention group versus placebo group ($p < 0.05$). These findings are quite profound because the authors of the present disclosure have described a surprisingly link between the effect of the cranberry product of the invention, the abundance of *Gardnerella* and the development of UTI and recurrent UTI.

[0005] *Gardnerella vaginalis* is a species of Gram-variable-staining facultative
30 anaerobic bacteria. The organisms are small (1.0–1.5 μm in diameter) non-spore-forming, nonmotile coccobacilli.

[0006] Once classified as *Haemophilus vaginalis* and afterwards as *Corynebacterium vaginalis*, *G. vaginalis* is a facultatively anaerobic Gram-variable rod that is involved, together with many other bacteria, mostly anaerobic, in bacterial vaginosis in some women as a result of a disruption in the normal vaginal microflora. *Gardnerella* is a
5 common and often dominant member of the vaginal microbiome, especially in the context of dysbiosis (Morrill, Sydney, Nicole M. Gilbert, and Amanda L. Lewis. "*Gardnerella vaginalis* as a cause of bacterial vaginosis: appraisal of the evidence from in vivo models." *Frontiers in cellular and infection microbiology* 10 (2020): 168).

[0007] Urine is the second most common source of isolation of *Gardnerella* after the
10 vagina.

[0008] As mentioned before, the inventors of the present invention have surprisingly observed a significant lower relative abundance of *Gardnerella* in the urinary microbiome of women after 6 months of treatment with the cranberry fruit product of the invention group versus placebo group ($p < 0.05$).

[0009] Thus, in a first aspect, the present invention relates to a cranberry fruit product according to the invention for use in a method for reducing and/or inhibiting the growth of microorganisms of the genus *Gardnerella* in the urinary tract of a human or animal subject.
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[0010] In a second aspect, the present invention relates to a method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a cranberry fruit product according to the invention.
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[0011] Indeed, it was described, that women with bacterial vaginosis caused by overgrowth of anaerobic species, such as some strains belonging to *Gardnerella vaginalis*, suffer more UTI than women with healthy microbial communities, composed mainly of *Lactobacillus* (Sumati, A. H., and N. K. Saritha. "Association of urinary tract infection in women with bacterial vaginosis." *Journal of global infectious diseases* 1.2 (2009): 151.).
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[0012] Therefore, in a third aspect, the present invention relates to a cranberry fruit product according to the invention for use in the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject.
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[0013] In a fourth aspect, the present invention relates to a cranberry fruit product according to the invention for use in delaying the occurrence of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject.

- 5 [0014] In a further aspect, the present invention relates to a non-therapeutic method of decreasing the population of *Gardnerella* in the urinary tract of a human or animal subject, the method comprising administering to the subject an effective amount of a cranberry fruit product according to the invention.

[0015] Moreover, it has been shown in animal models that temporary exposures to some
10 strains of *Gardnerella vaginalis* increased susceptibility to subsequent UTI cause by uropathogenic *E. coli*.

[0016] It was shown that *Gardnerella* bladder exposure induced urothelial apoptosis and exfoliation and activates host transcriptional pathways related to mucosal inflammation and immunity. Main mechanism of action consider is that urothelial
15 exfoliation would trigger activation of *E. coli* from dormant intracellular reservoirs in the bladder, enhancing the chance of developing UTI. (Gilbert, Nicole M., Valerie P. O'Brien, and Amanda L. Lewis. "Transient microbiota exposures activate dormant *Escherichia coli* infection in the bladder and drive severe outcomes of recurrent disease." *PLoS pathogens* 13.3 (2017): e1006238.; Gilbert, Nicole M., et al. "*Gardnerella*
20 exposures alter bladder gene expression and augment uropathogenic *Escherichia coli* urinary tract infection in mice." *Frontiers in cellular and infection microbiology* 12 (2022): 909799.)

[0017] Therefore, in a further aspect, the present invention relates to the composition for use, the method, or the non-therapeutic method according to any one of the preceding
25 aspects, wherein the treatment results in the inhibition of the activation and / or growth of *Escherichia coli* in the bladder of the subject

[0018] In a further aspect, the present invention relates to a method for determining whether a human or animal subject is likely to develop an UTI or a recurrent UTI, wherein the method comprises:

- 30 [0019] a) determining the abundance of *Gardnerella* in a urine sample of the subject

[0020] b) comparing the abundance of *Gardnerella* in at least a first control sample or population of control samples,

[0021] c) where the abundance of *Gardnerella* of the sample obtained from the subject is substantially similar to or higher than the abundance of *Gardnerella* in at least a first control sample or population of control samples, the subject is considered likely develop UTI,

5 optionally wherein where the abundance of *Gardnerella* of the sample obtained from the subject is at least 5% greater, such as at least 10% greater, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, at least 100% greater, such as at least 200% greater than the abundance of *Gardnerella* in at least a first control sample or population of control samples, the subject is considered to be likely to develop an UTI or a recurrent
10 UTI.

[0022] DESCRIPTION OF THE FIGURES

[0023] Figure 1: Bacterial genera present in the urine samples of all the women included in the study at baseline. X-axis: Prevalence (%). Y-axis: Relative abundance.

[0024]

15 [0025] DESCRIPTION OF THE INVENTION

[0026] The authors of the invention have discovered that in a randomized, parallel, double-blind, placebo controlled study of 150 women with history of recurrent UTIs, a significant reduction of the incidence of culture-positive UTIs was observed after 6 months of supplementation with the cranberry composition of the invention compared to
20 placebo (-52% of relative risk of UTI, $p = 0.01$). In parallel a significant lower relative abundance of *Gardnerella* was observed in the urinary microbiome of women in the group with administration of cranberry composition of the invention (at 6 months) versus placebo group ($p < 0.05$).

Also, the authors of the preset invention have surprisingly found that the treatment with
25 the cranberry product of the invention results in reduction of symptoms of urgency and frequency.

[0027] The present disclosure is related to a cranberry fruit product (or product of the invention) and the uses thereof.

[0028] In a first aspect, the present invention relates to a cranberry fruit product for use
30 in a method for reducing and/or inhibiting the growth of microorganisms of the genus *Gardnerella* in the urinary tract of a human or animal subject.

[0029] In a further aspect, the present invention relates to a method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a cranberry fruit product.

5 [0030] In another aspect, the present invention relates to a non-therapeutic method (hereinafter “the non-therapeutic method of the invention”) of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to the subject an effective amount of a cranberry fruit product.

[0031] In another aspect, the present invention relates to a therapeutic method (hereinafter
10 “the therapeutic method of the invention”) of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to the subject an effective amount of a cranberry fruit product.

[0032] The cranberry fruit product used in the present disclosure may be a cranberry juice, a cranberry puree, a cranberry powder, a cranberry extract or a combination thereof.
15 The cranberry fruit product used in the present invention may be obtained from the whole fruit, and/or skin of the cranberry fruit, and/or the pulp, and/or the pomace (or press cake) and/or the seeds and/or the residues of the fruit after juicing of the fruit. The fruit or the parts of the fruits may be fresh, frozen or dried. Juice that is recovered from any processing of the fruit may also be processed to recover a cranberry fruit product or
20 extract.

[0033] In one embodiment, the cranberry is *Vaccinium macrocarpon*. In some embodiments, the cranberry is *Vaccinium microcarpon*. In some embodiments, the cranberry is *Vaccinium oxycoccus*. In other embodiment, the cranberry fruit product may be obtained from one or more of *Vaccinium macrocarpon*, *Vaccinium microcarpon*,
25 *Vaccinium oxycoccus* or from mixtures thereof.

[0034] In one embodiment, the cranberry fruit product may be cranberry extract. The extract obtained from the cranberries may be an aqueous extract, an alcohol extract (which includes hydro-alcoholic extracts) or an organic extract.

[0035] The term “aqueous extract” as used herein, refers to the extract obtained from
30 cranberry (or cranberry pomace or cranberry puree) when the extraction from the fruit has been performed using water as the only solvent. Enzymes may be used in the process.

[0036] The term “alcohol extract” as used herein, refers to the extract obtained from cranberries when the extraction from the fruit has been performed using an alcohol as the solvent. The alcohol solvent may consist of only alcohol (e.g. 100% alcohol), for example 100% ethanol, or may be a mixture of an alcohol and water (i.e. a hydro-alcoholic solvent), for example, a mix of ethanol and water (hydro-ethanolic solvent), for example, from about 1% to about 99% alcohol (e.g. ethanol) in water, for example the ratio of water to alcohol is from 10/90% v/v to 90/10% v/v or 30/70% v/v to 70/30% v/v, such as 50/50% v/v or 70/30 v/v.

[0037] The term “organic extract” as used herein, refers to the extract obtained from cranberries when the extraction has been performed using an organic solvent that is not an alcohol. For example, the organic solvent may be selected from the group consisting of acetic acid, acetone, acetonitrile, benzene, 2-butanone, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethane, diethylene glycol, diethyl ether, diglyme (diethylene glycol, dimethyl ether), 1,2-dimethoxy-ethane (glyme, DME), dimethyl- formamide (DMF), dimethyl sulfoxide (DMSO), 1,4-dioxane, ethyl acetate, ethylene glycol, glycerin, heptane, hexamethylphosphoramide (HMPA), hexamethylphosphorous, triamide (HMPT), hexane, methyl t-butyl, ether (MTBE), methylene chloride, N-methyl-2-pyrrolidinone (NMP), nitromethane, pentane, petroleum ether (ligroine), pyridine, tetrahydrofuran (THF), toluene, triethyl amine, o-xylene, m-xylene and p-xylene.

[0038] In one embodiment, the cranberry fruit extract may be an aqueous extract of cranberry. In another embodiment the cranberry fruit product may be a purified cranberry extract.

[0039] The cranberry fruit product may be in the form of a liquid or in the form of a powder.

[0040] In one embodiment, the cranberry fruit product may be enriched with cranberry seeds or cranberry seed meal. The seeds or seed meal concentration may be of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the total cranberry fruit product. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of the total cranberry fruit product, such as from 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18% 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% to 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%,

27%, 26%, 25%, 24%, 23%, 22%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, of seeds or seed meal by weight of the total cranberry fruit product such as from 10% to 25%, such as 20% of seeds or seed meal by weight of the total cranberry fruit product.

5 [0041] In one embodiment, the cranberry fruit product is or comprises a dried cranberry powder. In the present invention a “dried cranberry powder” means a dried powder obtained from cranberry juice and/or a cranberry puree and/or pomace (or press cake) and/or whole cranberry fruits and/or a cranberry extract.

[0042] In certain embodiments the dried cranberry powder may be obtained from a
10 cranberry juice.

[0043] In certain embodiments the dried cranberry powder may be obtained from a cranberry extract.

[0044] In certain embodiments the dried cranberry powder may be obtained from a cranberry puree.

15 [0045] In certain embodiments the dried cranberry powder may be obtained from a cranberry pomace (or press cake).

[0046] In certain embodiments the dried cranberry powder may be obtained from whole cranberry fruits.

[0047] In certain embodiments the dried cranberry powder may be obtained from one
20 or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and whole cranberry fruits.

[0048] In one embodiment, the cranberry fruit product (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and whole cranberry fruits) may be enriched with
25 cranberry seeds or cranberry seed meal. The seeds or seed meal concentration may be of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the total cranberry fruit product. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of the total cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of the total cranberry fruit product.

30 [0049] In certain embodiments, the cranberry fruit product is a combination of a cranberry extract and cranberry seeds or seed meal. In certain embodiments, the seeds or

seed meal concentration may be of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the total cranberry fruit product. In certain embodiments, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of the total cranberry fruit product.

[0050] In certain embodiments, the cranberry fruit product of the invention is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits) that is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

[0051] In certain embodiments, the invention relates to a cranberry fruit product for use in a method for reducing and/or inhibiting the growth of microorganisms of the genus *Gardnerella* in the urinary tract of a human or animal subject, wherein the cranberry fruit product of the invention is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits). In certain preferred embodiments, the dried cranberry powder is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

[0052] In certain embodiments, the invention relates to a method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a cranberry fruit product, wherein the cranberry fruit product of the invention is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits). In certain preferred embodiments, the dried cranberry powder is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the

seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

5 [0053] In certain embodiments, the invention relates to a non-therapeutic method (hereinafter “the non-therapeutic method of the invention”) of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to the subject an effective amount of a cranberry fruit product, wherein the cranberry fruit product of the invention is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a
10 cranberry juice, a cranberry extract and/or whole cranberry fruits). In certain preferred embodiments, the dried cranberry powder is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20%
15 of seeds or seed meal by weight of dried cranberry powder.

[0054] In certain embodiments, the invention relates to a therapeutic method (hereinafter “the therapeutic method of the invention”) of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to the subject an effective amount of a cranberry fruit product, wherein the cranberry fruit product of the
20 invention is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits). In certain preferred embodiments, the dried cranberry powder is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder.
25 In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

[0055] In certain embodiments, the cranberry fruit product of the invention is prepared as described in WO2015070203A1 which disclosure is incorporated by reference.

30 [0056] In certain embodiments, the cranberry product of the invention is produced by the following method: a) one or more of a cranberry puree, a cranberry pomace (or press

cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits are weighed and mixed to create a slurry,

b) optionally, if the composition is enriched in cranberry seeds or seeds meal, seeds or seeds meal are added to the slurry,

5 c) the slurry is dried

The drying is performed using any drying method suitable in the art.

In certain embodiments, optionally water may be added to the slurry before drying.

In certain embodiments, before drying, the slurry is passed through sieve or a mesh screen (such as a 14 mesh screen) or any other means that allow to remove bigger particles.

10 Additionally, the slurry may be sheared, dried and milled.

In certain embodiments, the milled composition is passed through a sieve, sealed and pelletized.

[0057] In certain preferred embodiments, the seeds (or seeds meal) are added so as to arrive at a concentration of seeds of about $20\pm 5\%$ by weight of the dried cranberry powder.

[0058] The cranberry fruit product of the invention may be characterized as described in WO2015070203A1 which disclosure and methods disclosed are incorporated herein by reference. The organic acid profile, the sugar content, the concentration of proanthocyanidins and the concentration of anthocyanins of the cranberry fruit product of the invention may be measured as described in WO2015070203A1 and are incorporated herein by reference. Organic acids may be measured using a modified AOAC (986.13) entitled Quinic, Malic and Citric Acids in Cranberry Juice Cocktail and Apple Juice as described in example 2 of WO2015070203A1, which disclosure is incorporated here by reference.

25 [0059] Sugar contain may be measured using a modified AOAC method 977.20 as described in example 2 of WO2015070203A1, which disclosure is incorporated here by reference.

[0060] Concentration of proanthocyanidins may be measured using BL-DMAC assay as described in example 2 of WO2015070203A1 and in (Prior et al., "Multi-laboratory validation of a standard method for quantifying proanthocyanidins in cranberry powders" J Sci Food Agric. 90:1473-8 (2010)), which disclosure is incorporated here by reference.

Concentration of proanthocyanidins may also be measured by HPLC-fluorescence using a Develosil Diol or equivalent and analyzed by HPLC-UV at a wavelength of 535 nm as described in example 2 of WO2015070203A1, which disclosure is incorporated here by reference.

- 5 [0061] Rest of phenolics may be analyzed by UPLC-MS/MS using the method described in example 2 of WO2015070203A1, which disclosure is incorporated here by reference.

Lignans are analyzed by UPLC-MS/MS using a 2.1mm x 150mm ACQUITY BEH C18 reverse phase 1. 7µm particle size column, as described in example 2 of
10 WO2015070203A1, which disclosure is incorporated here by reference.

[0062] In some embodiments, the cranberry fruit product of the invention comprises less than about 12% of organic acids by weight, in some embodiments, the composition comprises less than 10% of organic acids by weight. In some embodiments, the composition comprises about 5% to about 8% of organic acids

- 15 [0063] In some embodiments, the cranberry fruit product comprises less than about 15% of sugars by weight, such as less than 12% or less than 10 % of sugars by weight.

[0064] In some embodiments, the cranberry fruit product comprises from about 1 % to about 5% of quinic acid by weight. According to certain illustrative embodiments, the cranberry fruit product comprises from about 2.2% to about 3.2% of quinic acid by
20 weight.

[0065] In some embodiments, the cranberry fruit product comprises from about 0.4% to about 4% of malic acid by weight.

[0066] In some embodiments, the cranberry fruit product comprises from about 1 % to about 5% of citric by weight. According to certain illustrative embodiments, the cranberry
25 fruit product comprises from about 1.8% to about 3.2% of citric acid by weight.

[0067] In one embodiment, the cranberry fruit product has from about 0.1% (w/w) to 30% w/w proanthocyanidins according to the BL-DMAC assay, such as from about 1% to 30%, such as from about 0.2% to about 20%, or such as from about 0.3% to 15%, or 0.25% to 1% wt/wt, such as more than 0.3 w/w according to the BL-DMAC assay.

- 30 [0068] In one embodiment, the cranberry fruit product has more than 1.5% (w/w) proanthocyanidins, according to HPLC, such as from about 1% to 30% such as from about

0.2% to about 20%, or such as from about 1% to 15%, or 1.5% to 10% w/w according to HPLC assay. In certain embodiments, the cranberry fruit product comprises more than 0.3% (w/w) proanthocyanidins according to the BL-DMAC assay or more than 1.5% (w/w) proanthocyanidins according to HPLC. In one embodiment, the total phenolic
5 of the cranberry component is from about 10% to about 60%, such as from about 20% to about 30% wt/wt.

[0069] In some embodiments, the cranberry fruit product comprises 0.5% to 5.0% proanthocyanidins, 0.05% to 1.5% quercetin, 0.001 % to 0.1 % quercetin-3-glucoside, 0.001 % to 0.1 % quercetin-3- rhamnoside, 0.001 % to 0.1 % quercetin-3-xyloside, 0.001
10 % to 0.1 % quercetin-3-arabinoside, 0.001 % to 0.5% myricetin, 0.001 % to 0.1 % peonidin-3-galactoside, 0.001 % to 0.1 % peonidin-3- glucoside, 0.001 % to 0.1 % peonidin-3-arabinoside, 0.001 % to 0.1 % cyanidin-3-glucoside, 0.001 % to 0.1 % cyanidin-3-galactoside, 0.001 % to 0.1 % cyanidin-3-arabinoside, 0.001 % to 0.1 % protocatechuic acid 0.001 % to 0.1 % p-coumaric acid, 0.001 % to 0.1 % caffeoyl-
15 glucoside, 0.001 % to 0.1 % coumaroyl-glucoside, 0.001 % to 0.1 % caffeic acid, 0.001 % to 0.1 % chlorogenic acid or 0.01 to 1.5% ursolic acid by weight.

[0070] In some embodiments, the cranberry fruit product comprises 1.0% to 1.2% proanthocyanidins, 0.16% to 0.20% quercetin, 0.07% to 0.09% quercetin-3-glucoside, 0.03% to 0.04% quercetin-3- rhamnoside, 0.019% to 0.025% quercetin-3-xyloside, 0.025% to 0.035% quercetin-3-arabinoside, 0.010% to 0.014% myricetin, 0.022% to
20 0.030% peonidin-3-galactoside, 0.0025% to 0.0035% peonidin-3-glucoside, 0.010% to 0.020% peonidin-3-arabinoside, 0.0005% to 0.0015% cyanidin-3- glucoside, 0.015% to 0.030% cyanidin-3-galactoside, 0.010% to 0.025% cyanidin-3-arabinoside, 0.019% to 0.025% protocatechuic acid, 0.04% to 0.06% p-coumaric acid, 0.015% to 0.025%
25 caffeoyl-glucoside, 0.005% to 0.015% coumaroyl-glucoside, 0.010% to 0.015% caffeic acid or 0.030% to 0.04% chlorogenic acid by weight.

[0071] In some embodiments, the cranberry fruit product comprises about 1.1 % proanthocyanidins, 0.18% quercetin, 0.083% quercetin-3-glucoside, 0.034% quercetin-3-rhamnoside, 0.022% quercetin-3-xyloside, 0.030% quercetin-3-arabinoside, 0.012%
30 myricetin, 0.027% peonidin-3- galactoside, 0.003% peonidin-3-glucoside, 0.014% peonidin-3-arabinoside, 0.001 % cyanidin-3- glucoside, 0.022% cyanidin-3-galactoside, 0.018% cyanidin-3-arabinoside, 0.022% protocatechuic acid, 0.052% p-coumaric acid,

0.021 % caffeoyl-glucoside, 0.011 % coumaroyl-glucoside, 0.014% caffeic acid, 0.034% chlorogenic acid or 0.92% ursolic acid by weight.

[0072] In some embodiments, the cranberry fruit product comprises 1 to 100 µg lariciresinol, 1 to 100 µg secoisolariciresinol or 1 to 100 µg/ pinoresinol per 100 g of the composition by weight.

[0073] In some embodiments, the cranberry fruit product comprises about 51 µg lariciresinol, about 12 µg secoisolariciresinol or about 78 µg/ pinoresinol per 100g of the composition by weight.

[0074] In another particular embodiment, the cranberry fruit product contains at least 0,5% of total fiber. In a more particular embodiment, the cranberry fruit extract contains between 0,5% and 10% of total fiber.

[0075] In another aspect, is provided a method modulating or adjusting urinary tract microbiome and/or reverting urinary tract microbiome dysbiosis in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a cranberry fruit product.

[0076] Dysbiosis is often defined as an “imbalance” in for example the urinary microbial community that is associated with disease. This imbalance could be due to the gain or loss of community members or changes in relative abundance of microbes.

The terms “microbiome” refers to the collection of genomes from all the micro-organisms in the environment, meaning the collection of all their genetic material (DNA and RNA). Also includes the microorganisms to which the genetic material corresponds.

In the present invention, the term "subject" refers to any animal of any species. Preferably the subject is a mammal. More preferably the subject is a human. In certain embodiments, the subject is a female. In certain embodiments, subject is a male. In certain embodiments the subject is an animal such as a companion animal (domesticated animals). In one aspect the animal can be a mammal. In one aspect, the animal can be a canine. In another aspect, the companion animal can be a canine and/or a feline.

[0077] As mentioned above, the authors of the present invention have surprisingly discovered that the cranberry fruit product of the invention significantly decreases the population of *Gardnerella* in the urinary tract of a subject. This reduction was linked to a significant reduction of the incidence of culture-positive UTIs that was observed after 6

months of supplementation with the cranberry fruit product of the invention. This was also linked to the reduction of symptoms of urgency and frequency in women with confirmed UTIs.

5 [0078] Therefore, in another aspect, it is provided a method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a cranberry fruit product of the invention.

10 [0079] In certain embodiments, there is described a method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a cranberry fruit product of the invention, wherein the cranberry fruit product of the invention is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits). In certain preferred embodiments, the dried cranberry powder is
15 enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

20 [0080] In certain embodiments, the treatment results in the prevention of urinary tract infections (UTI).

In certain embodiments, the treatment results in reduction of symptoms of urgency and frequency.

25 [0081] In another aspect, it is provided a cranberry fruit product for use in the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject.

30 [0082] In another aspect, it is provided a cranberry fruit product for use in the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject, wherein the cranberry fruit product is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits). In certain preferred embodiments, the

dried cranberry powder is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

[0083] The term "urinary tract infections" refers to common infections that happen when bacteria, often from the skin or rectum, enter the urethra, and infect the urinary tract. The infections can affect several parts of the urinary tract, but the most common type is a bladder infection (cystitis). The leading cause of UTI is the pathogenic bacteria *Escherichia coli*. *E. coli* bacteria gain entrance to the urinary tract, use their hair-like fimbriae to build a biofilm or protective colony and eventually form an infection. Recurrent UTIs are defined as at least three episodes of UTIs in the last twelve months or at least two episodes of UTIs in the last six months.

[0084] In certain embodiments, the UTI is a "culture-positive UTI" or "culture-confirmed UTI".

[0085] "Culture-positive UTI" or "culture-confirmed UTI" refers to UTI present in subjects who experienced UTI symptoms (dysuria, fever, urinary frequency, urinary urgency, suprapubic pain, haematuria), and where a culture confirmation of the urines was done and the results showed a bacterial growth of $>10^8$ colony-forming units (cfu) /L (10^5 cfu/mL) of microorganisms, typically uropathogenic *E. coli*, but occasionally other pathogens such as for example *Enterococci*, *Enterobacter spp.*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus*.

[0086] Culture of urines is a standard analytical procedure. (Anger, Jennifer, et al. "Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline." The Journal of urology 202.2 (2019): 282-289.; European Medicines Agency. Evaluation of medicinal products indicated for treatment of bacterial infections. 2022. Available at: <https://www.ema.europa.eu/en/evaluation-medicinal-products-indicated-treatment-bacterial-infections>. Accessed 27 July 2023. and FDA 2019 guidelines US Food and Drug Administration. Uncomplicated urinary tract infections: developing drugs for treatment guidance for industry. 2019. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/uncomplicated-urinary-tract-infections>

developing-drugs-treatment-guidance-industry. Accessed 27 July 2023) for example using the following method:

5 [0087] A mid-stream urine sample was collected for dipstick, urinalysis and culture. Briefly, following hand washing and wiping of the labia, a small amount of urine was first passed into the toilet, and then collected into the specimen pot until $\frac{3}{4}$ full, with the remaining urine passed into the toilet.

[0088] Uropathogenic species that are usually determined within the urine sample include notably the following major uropathogens: *Escherichia coli*, *Enterococci*, *Enterobacter* spp., *Staphylococcus saprophyticus*, *Klebsiella* spp., *Citrobacter* spp.,
10 Group B *Streptococcus*, other gram-negative rods, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Dipstick urinalysis included assessment of nitrite, leucocyte esterase, pH, specific gravity, protein, glucose, ketones, urobilinogen, bilirubin, and blood.

[0089] In certain embodiments of the uses or methods of the invention, the treatment results in the prevention and/or the treatment of recurrent UTI.

15 [0090] In certain embodiments of the uses or methods of the invention, the treatment results in the reduction of UTI symptoms such as urgency and frequency

[0091] In some embodiments, the infection is genitourinary infection.

[0092] In some embodiments, the infection is caused by antimicrobial sensitive bacteria.

[0093] In some embodiments, the infection is caused by antimicrobial resistant bacteria.

20 [0094] In some embodiments, the uses or the method does not comprise administering an antimicrobial agent to the human or animal.

[0095] In some embodiments, the method comprises combining the composition with an antimicrobial agent and administering to the human or animal.

25 [0096] In some embodiments, the method comprises combining the composition with a probiotic and administering to the human or animal.

[0097] In some embodiments, the infection is selected from *H. pylori* infection, cystic fibrosis, bacteremia, sepsis, yeast infections, bacterial vaginosis, and/or prostatitis (including bacterial prostatitis).

In some embodiments of the methods or uses of the present invention, the cranberry fruit product of the present disclosure may be formulated as a composition comprising the cranberry fruit product.

5 In some embodiments of the methods or uses of the present invention, the cranberry fruit product of the present disclosure may be formulated as a pharmaceutical composition or the nutraceutical composition.

[0098] The composition, broadly defined, is a set of components consisting of at least the cranberry fruit product of the invention as defined previously. The composition may comprise other components such as, for example, inert substances or bioactive
10 components.

[0099] In some embodiments, the cranberry fruit product of the invention or the composition comprising the cranberry fruit product of the invention is formulated as a solid oral dosage such as a tablet, a capsule, or a softgel. In some embodiments, such solid oral dosage comprises from 50 mg to 1500 mg of the cranberry fruit product of the
15 invention, e.g., 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 800mg, 900mg, 1000 mg or 1500 mg.

[0100] Solid dosage forms comprising the compositions described herein optionally comprise a suitable amount of one or more pharmaceutically acceptable excipients so as to provide the form for proper administration to the subject.

20 [0101] Such pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one
25 embodiment, the pharmaceutically acceptable excipients are sterile when administered to a subject. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol and the like. The present therapeutic compositions, if desired, can also contain minor amounts of
30 wetting or emulsifying agents, or pH buffering agents. In one embodiment, the composition is in the form of a capsule (see, e.g., U.S. Patent No. 5,698,155). Other

examples of suitable pharmaceutical excipients are described in Remington's Pharmaceutical Sciences 1447-1676 (Alfonso R. Gennaro eds., 19th ed. 1995).

- [0102]** In some embodiments, the cranberry fruit product of the invention or the composition described herein is formulated in accordance with routine procedures as a composition adapted for oral administration to human beings (such as a pharmaceutical composition or a nutraceutical composition). Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, softgels, syrups, or elixirs for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active therapeutic composition is also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate can also be useful. Oral compositions can include standard excipients such as mannitol, lactose, starch, maltodextrin, cyclodextrins, alginate, arabic or guar gum, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.
- [0103]** Pharmaceutical dosage forms for oral use can be obtained through combination of a therapeutic composition described herein with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or dragee cores. Suitable solid excipients in addition to those previously mentioned are carbohydrate or protein fillers that include, but are not limited to, sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen.

Maltodextrin and cyclodextrins can also be used. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

5 [0104] Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredients is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

[0105] Softgels for oral use may consist of a gelatin based shell surrounding a liquid fill. Softgel shells can be made of a combination of gelatin, water, opacifier and a plasticiser such as glycerin and/or sorbitol.

10 [0106] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses. Therapeutic compositions described herein can be administered by controlled-release or sustained release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos. 5,674,533; 5,059,595; 5,120,548; 5,073,543; 5,639,476 and 5,354,556, each of which is incorporated herein by reference in its entirety.

20 Such dosage forms can be useful for providing controlled or sustained release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled or sustained release formulations known to those skilled in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The present disclosure thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled or sustained release.

30 [0107] Controlled or sustained release compositions can initially release an amount of an active ingredient present in the therapeutic composition that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other

amounts of the active ingredients present in the therapeutic composition to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of an active ingredient present in the therapeutic composition in the body, active ingredients present in the therapeutic composition thereof can be released from the dosage form at a rate that will replace the amount of the active ingredients present in the therapeutic composition being metabolized and excreted from the body. Controlled or sustained release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

[0108] The amount of the cranberry fruit product of the invention that is useful for treating UTI, or that is useful for decreasing the population of *Gardnerella* in the urinary tract of a subject, or that is useful for the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject as described before can be determined by standard clinical techniques.

[0109] The amount of the cranberry fruit product of the invention, the composition of the present disclosure (comprising a cranberry fruit product of the invention), the pharmaceutical composition or the nutraceutical composition that is useful for treating UTI, or that is useful for decreasing the population of *Gardnerella* in the urinary tract of a subject, or that is useful for the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject as described before can be determined by standard clinical techniques. In addition, in vitro or in vivo assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed can also depend on the route of administration, and the seriousness of the condition being treated and can be decided according to the judgment of the practitioner and each subject's circumstances in view of, e.g., published clinical studies. Suitable effective dosage amounts, however, range from about 50 mg to about 5 grams about every 24 hours, although they are typically about 500 mg or less per every 24 hours. In one embodiment, the effective dosage is about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1 g, about 1.2 g, about 1.4 g, about 1.6 g, about 1.8 g, about 2.0 g,

about 2.2 g, about 2.4 g, about 2.6 g, about 2.8 g, about 3.0 g, about 3.2 g, about 3.4 g, about 3.6 g, about 3.8 g, about 4.0 g, about 4.2 g, about 4.4 g, about 4.6 g, about 4.8 g, and about 5.0 g, every 24 hours. Equivalent dosages can be administered over various time periods including, but not limited to about every 2 hours, about every 4 hours, about every 6 hours, about every 8 hours, about every 24 hours, about every 36 hours, about every 48 hours, about every 72 hours, about every week, about every two weeks, about every three weeks, about every month, and about every two months. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one therapeutic composition is administered, the effective dosage amounts correspond to the total amount administered.

[0110] The cranberry fruit product of the invention or the compositions described herein can be administered as long as the symptoms persist or longer. The cranberry fruit product of the invention or the compositions described herein can be administered to prevent the symptoms and conditions already defined in the present disclosure. In some embodiments, the therapeutic composition is administered for 3, 4, 5, 6 days, one week, two weeks, three weeks, one month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more.

[0111] The dosage regimen utilizing the therapeutic or nutraceutical compositions described herein can be selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the subject; the severity of the condition to be treated; the route of administration; and the renal or hepatic function of the subject.

[0112] A therapeutic or nutraceutical composition described herein can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily.

[0113] In a particular embodiment, the compositions may further comprise at least one bioactive component (active substance, active principle or therapeutic agent), such as for example other food components, plant or fungal products and/or pharmaceuticals.

[0114] The term "bioactive component" refers to a compound with biological activity within the scope of the patent that may enhance or complement the activity of the cranberry fruit extract, including food ingredients or components, probiotics, plants, fungi, extracts or components of plants, fungi and pharmaceuticals.

[0115] The composition of the invention may be formulated (i) for dietary administration, i.e. on its own or as part of the food consumed in the diet of the subject, (ii) for cosmetic administration, i.e. on its own or as part of cosmetic products or (iii) for cosmeceutical administration, i.e. on its own or as part of cosmetic products administered to the subject by any means of administration.

[0116] In another particular aspect, the present invention relates to a nutraceutical composition which comprises a cranberry fruit product as defined previously. The term “nutraceutical composition” refers to foods or naturally occurring food supplements intended for human ingestion, that have medical or health benefits, including the prevention and treatment of a disease. The nutraceutical composition may be a food or incorporated into a food or foodstuff intended for human and/or animal consumption. Thus, in a particular embodiment, the nutraceutical composition is a food or a nutritional supplement.

[0117] In some particular embodiments, the nutraceutical composition of the invention is a food for specific nutritional purposes. In some specific embodiments, the nutraceutical composition of the invention is a food for special medical purposes. Foods for special medical purposes are those foods that have been specially prepared or formulated for the dietary management of patients under medical supervision. These foods are intended to meet all or part of the dietary needs of patients.

[0118] Examples of foods that may comprise the nutraceutical composition include, but are not limited to, animal feed, dairy products, vegetable products, meat products, snacks, chocolates, beverages, baby food, cereals, fried foods, industrial bakery products and biscuits. Examples of dairy products include, but are not limited to, fermented milk products (e.g., but not limited to, yoghurt or cheese) or non-fermented milk (e.g., but not limited to, ice cream, butter, margarine or whey). The plant product is, for example, but not limited to, a cereal in any form of presentation, fermented (e.g., soy yoghurt, oat yoghurt, etc.) or unfermented. Beverages include, but are not limited to, any fruit juice or non-fermented milk.

[0119] In another particular aspect, the present invention relates to a cosmeceutical composition, which comprises a cranberry fruit product. The term “cosmeceutical composition” as used herein refers to a cosmetic composition that have medicinal or drug-like benefits. This composition has both cosmetic and pharmaceutical properties. The

term “drugs” refer to products that cure, treat, mitigate or prevent disease or that affect the structure or function of the human body. The term “pharmaceutical properties” refers to the improvement of the physical or physiological or psychological well-being of a subject which implies an improvement in the general state of health or a reduction in the risk of disease.

[0120] The cranberry fruit product or the compositions can be administered orally, topically, parenterally, rectally, vaginally among others.

[0121] The presentation of the compositions will be adapted to the type of administration used. The compositions may be formulated in solid, semi-solid or liquid preparations, such as tablets, capsules, powders, granules, solutions, suppositories, gels, microspheres and/or any other form known in the food, medical device, cosmetic and/or pharmaceutical art. In a particular embodiment, the compositions are formulated for administration in solid or liquid form.

[0122] In another particular embodiment, the solid formulation is selected from the group consisting of tablets, lozenges, candies, chewable tablets, chewing gums, capsules, sachets, powders, granules, coated particles or coated tablets, tablets, pills, gastro-resistant tablets and capsules, and dispersible strips and films.

[0123] In another particular embodiment, the liquid formulation is selected from the group consisting of oral solutions, suspensions, emulsions and syrups.

[0124] Furthermore, various systems are known which can be used for sustained release administration of the compositions, including, without limitation, encapsulation in liposomes, microbubbles, microparticles or microcapsules and the like. Suitable sustained release forms, as well as materials and methods for their preparation, are well known in the prior art. Thus, the orally administrable form of the compositions is in a sustained release form further comprising at least one coating or matrix. The sustained release coating or matrix includes, without limitation, semi-synthetic or synthetic, water insoluble or modified natural polymers, waxes, fats, fatty alcohols, fatty acids, natural, semi-synthetic or synthetic plasticisers or a combination of two or more thereof. Enteric coatings can be applied by conventional processes known to the person skilled in the art.

[0125] In addition to what is described above, the present invention also covers the possibility that the compositions may be administered to a subject together with other components or compounds, even if these do not form part of the composition.

5 [0126] In another particular aspect, the present invention relates to a food supplement which comprises a cranberry fruit product for use in the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject.

10 [0127] In another particular aspect, the present invention relates to a food supplement which comprises a cranberry fruit product for use in the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject, wherein the cranberry fruit product is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits). In certain preferred embodiments, the dried cranberry powder is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

20 [0128] The present invention relates to a food supplement which comprises a cranberry fruit product for use in a method for reducing and/or inhibiting the growth of microorganisms of the genus *Gardnerella* in the urinary tract of a human or animal subject.

25 [0129] The present invention relates to a food supplement which comprises a cranberry fruit product for use in a method for reducing and/or inhibiting the growth of microorganisms of the genus *Gardnerella* in the urinary tract of a human or animal subject, wherein the cranberry fruit product is a dried cranberry powder (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits) . In certain embodiments, the dried cranberry powder is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one embodiment, the seeds or seed meal concentration may be

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from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

5 [0130] The present invention relates to a method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a food supplement comprising cranberry fruit product as described in the present invention. The term “food supplement” refers to products or preparations intended to supplement the normal diet of a subject and consisting of *concentrated* nutrient sources or other substances with a nutritional or physiological effect.

10 [0131] In another particular aspect, the present invention relates to a dietary supplement which comprises a cranberry fruit product for use in the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject.

15 [0132] The present invention relates to a dietary supplement comprising a cranberry fruit product for use in a method for reducing and/or inhibiting the growth of microorganisms of the genus *Gardnerella* in the urinary tract of a human or animal subject.

20 [0133] The present invention relates to a method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a dietary supplement comprising cranberry fruit product as described in the present invention.

25 [0134] In certain embodiments, the cranberry fruit product of the invention present in the dietary supplement, or the food supplement, is a dried whole cranberry power (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits).

30 [0135] In certain embodiments, the cranberry fruit product of the invention present in the dietary supplement, or the food supplement, is a dried cranberry power (such as a dried cranberry powder obtained from one or more of a cranberry puree, a cranberry pomace (or press cake), a cranberry juice, a cranberry extract and/or whole cranberry fruits) that is enriched with cranberry seeds or seed meal at a concentration of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder. In one

embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of cranberry fruit product, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of dried cranberry powder.

5 [0136] The term “dietary supplement” refers to a manufactured product intended to supplement the dietary needs of patients and that provides health benefits to the subjects.

The food supplement or the dietary supplement may be in single or combined form and marketed in dosage form, i.e. in capsules, pills, tablets and other similar forms, powder sachets, liquid ampoules and drop dispensing bottles and other similar forms of liquids and powders designed to be taken in a single quantity.

10 [0137] In some embodiments, the cranberry fruit product of the present disclosure, the composition comprising the cranberry fruit product of the present disclosure, the pharmaceutical composition or the nutraceutical composition may comprise or may be used in combination with a non-steroidal anti-inflammatory agent.

[0138] In some embodiments, the non-steroidal anti-inflammatory agent is ibuprofen.

15 [0139] In some embodiments, the cranberry fruit product of the present disclosure, the composition comprising the cranberry fruit product of the present disclosure, the pharmaceutical composition or the nutraceutical composition may comprise or may be used in combination with probiotics.

20 [0140] In some embodiments, the cranberry fruit product of the present disclosure, the composition comprising the cranberry fruit product of the present disclosure, the pharmaceutical composition or the nutraceutical composition may comprise or may be used in combination with an antimicrobial agent.

25 [0141] In some embodiments, the cranberry fruit product of the present disclosure, the composition comprising the cranberry fruit product of the present disclosure, the pharmaceutical composition or the nutraceutical composition does not comprise an antimicrobial agent.

30 [0142] In some embodiments, the cranberry fruit product of the present disclosure, the composition comprising the cranberry fruit product of the present disclosure, the pharmaceutical composition or the nutraceutical composition may comprise or may be used in combination with an anti-inflammatory agent.

[0143] In some embodiments, the antimicrobial agent is selected from the group consisting of β -lactam antimicrobial, carbapenems, penicillins, cephalosporins, oxacephems, monobactams, penems, cycloserine, fosfomycin, glycopeptides, lipoglycopeptides, polymyxins, rifamycins, ansamycins, actinomycins, tiacumycins, 5 quinolones, fluoroquinolones, aminocoumarins, lipamycins, sulfonamides, nitrofurantoin, nitrimidazole, aminoglycosides, tetracyclines, oxazolidinones, macrolides, thiopeptides, chloramphenicol, fusidic acid, clindamycin, lincosamides, glycylicyclines and beta-lactamase inhibitors.

[0144] In some embodiments, the probiotic agent is selected from the group consisting of 10 *Bacillus coagulans*, *Akkermansia muciniphila*, *Lactobacillus gasseri*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* GG, *Lactobacillus plantarum* 299V, *Saccharomyces boulardi*, *Bifidobacterium infantis*, *Lactobacillus casei*, *Lactobacillus crispatus*, *Lactobacillus reuteri*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus helveticus*, *Lactobacillus reuteri* 15 *protectis*, *Lactobacillus iners*, *Lactobacillus jensenii*, *Lactobacillus fermentum*, *Lactobacillus brevis*, *Lactobacillus casei*, *Lactobacillus vaginalis*, *Lactobacillus delbrueckii*, and *Lactobacillus salivarius*.

[0145] In some embodiments, the infection-causing bacterial strain is gram positive or gram negative.

20 [0146] In some embodiments, the composition of the present disclosure when used in combination with antimicrobials promotes shorter treatment duration and lower dosage of antimicrobials, sparing the healthy microbiome.

[0147] In some embodiments, the cranberry fruit product or the composition comprising said cranberry fruit product according to the present disclosure is used in prophylaxis to 25 avoid the need for antimicrobial treatment, sparing the healthy microbiome.

[0148] In a particular embodiment, the use of cranberry fruit product of the invention in the method or uses of the invention is associated with health benefits such as prevention and/or the treatment of recurrent UTI.

[0149] In a particular embodiment of the method or uses of the invention, the subject is 30 experiencing or is at risk of experiencing UTI.

[0150] In a particular embodiment of the method or uses of the invention, the use or method results in the prevention and/or the treatment of recurrent UTI.

[0151] The term "treatment" as used in the present invention refers to the treatment of a disease or medical condition in a subject, preferably human, comprising:

[0152] (a) preventing the onset of the disease or medical condition, i.e. prophylactic treatment of a subject;

5 [0153] (b) ameliorating the disease or medical condition, i.e. causing regression of the disease or medical condition in a subject;

[0154] (c) to suppress the disease or medical condition, i.e. to slow down the development of the disease or medical condition in a subject; or

[0155] (d) to alleviate the symptoms of the disease or medical condition in a subject.

10 [0156] The term "prevention" refers to preventing the occurrence of the disease, i.e. preventing the occurrence of the disease or pathological condition in a subject (preferably a mammal, and more preferably a human), in particular, where such a subject is predisposed to the pathological condition.

[0157] As used herein, the term "at risk for disease" refers to a subject (e.g., a human)
15 that is predisposed to experiencing a particular disease. This predisposition may be genetic (e.g., a particular genetic tendency to experience the disease, such as heritable disorders), or due to other factors (e.g., age, weight, environmental conditions, exposures to detrimental compounds present in the environment, etc.). Thus, it is not intended that the present invention be limited to any particular risk, nor is it intended that the present
20 invention be limited to any particular disease.

[0158] The term "recurrent UTI" means in the present disclosure at least three episodes of UTIs in the last twelve months or at least two episodes of UTIs in the last six months.

[0159] In a particular embodiment of the method or uses of the invention, the use or method results in the reduction of UTI symptoms such as urinary urgency and urinary
25 frequency.

[0160] The term "urinary urgency" means in the present disclosure complaint by the individual of a sudden, compelling desire to pass urine which is difficult to defer. The term "urinary frequency" means in the present disclosure complaint by the individual (or caregiver) that voiding occurs more frequently than deemed normal.

[0161] In a particular embodiment of the method or uses of the invention, the treatment results in the inhibition of the activation of *Escherichia coli* in the bladder.

[0162] The cranberry fruit product must be present in an effective amount to exert its effect on modulation of *Gardnerella* and on the treatment and/or prevention of UTI.

- 5 [0163] The term "effective amount" means any amount of the cranberry fruit product which, when administered to a subject, is sufficient to produce the desired effect. The effective amount may vary depending on, for example, the age, body weight, general health, sex and diet of the subject, as well as the mode and timing of administration. For example, an effective amount per day may be from about 100 mg to 5 g of the cranberry fruit product of the invention, such as from about 200 mg to 1000 mg, such as 500 mg of cranberry fruit product.

[0164] An effective amount per day may be from about 0.017 mg/kg of body weight (bw) to 83.33 mg/kg of bw, such as from about 3.33 mg/kg of bw to 16.67 mg/kg of bw, such as 8.33 mg/kg of bw.

- 15 [0165] In another aspect, the present invention relates to a method for determining whether a human or animal subject is likely to develop an UTI or a recurrent UTI, wherein the method comprises:

[0166] a) determining the abundance of *Gardnerella* in a urine sample of the subject

- [0167] b) comparing the abundance of *Gardnerella* in at least a first control sample or population of control samples,

[0168] c) where the abundance of *Gardnerella* of the sample obtained from the subject is substantially similar to or higher than the abundance of *Gardnerella* in at least a first control sample or population of control samples, the subject is considered likely develop UTI,

- 25 [0169] optionally wherein where the abundance of *Gardnerella* of the sample obtained from the subject is at least 5% greater, such as at least 10% greater, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, at least 100% greater, such as at least 200% greater than the abundance of *Gardnerella* in at least a first control sample or population

of control samples, the subject is considered to be likely to develop an UTI or a recurrent UTI.

The control samples are typically taken from subjects that are known to have a low level of *Gardnerella* and do not present UTI. For example, the control values used may be
5 obtain from Figure 1 of the present disclosure. The skilled person appreciates that for such methods the statistical power is greater the larger the sample size. Accordingly, in one embodiment the number of samples used from a subject with a low level of *Gardnerella* and no UTI is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18,
19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 or more
10 subjects.

[0170] EXAMPLES

[0171] Having now generally described the invention, the same will be more readily understood through reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

15 [0172] The authors of the present invention have investigated the biological effects of a cranberry fruit extract and impact of these products on the human urinary tract microbiome.

[0173] Cranberry product

[0174] The cranberry fruit product of the invention was prepared as described in
20 WO2015070203A1 which disclosure is incorporated by reference. Briefly, cranberry berries, skins, juice, puree and/or pomace are weighed and mixed to create a slurry. If the composition is enriched in cranberry seeds or seeds meal, seeds are added to the slurry. Water is added to the slurry. The slurry is passed through a 14 mesh screen, sheared, dried and milled. The milled composition is passed through a sieve, sealed and
25 pelletized. The seeds (or seeds meal) were added so as to arrive at a concentration of seeds of about $20 \pm 5\%$ by weight of the dried cranberry powder. The cranberry fruit product was characterized as described in WO2015070203A1 which disclosure is incorporated herein by reference. The organic acid profile, the sugar content, the concentration of proanthocyanidins and the concentration of anthocyanins of the cranberry fruit product
30 enriched in cranberry seeds or seeds meal used in the present example are described in WO2015070203A1 and are incorporated herein by reference.

[0175]

[0176] Clinical study

[0177] Healthy females (n=150, 18-65 years, body mass index (BMI) >17.5-<35 kg/m²) with a history of recurrent UTI (rUTI), defined as ≥3 UTIs in the last year or at least 2
5 UTIs in the last 6 months as confirmed by a health professional, were recruited across 5 Australian sites. Participants with a history of >5 UTIs in the last 6 months were excluded. Within a 6-month double-blind 1:1 randomised placebo-controlled multicentre clinical trial, participants consumed either 1 capsule (500 mg) per day of cranberry fruit product of the invention or placebo (soy oil). Incidence of UTI was assessed by pathology cultured
10 confirmation at a level of >10⁸CFU/L (10⁵CFU/mL) from mid-stream urine samples.

[0178] Participants attended the research clinic at baseline, 3- and 6-months. At any time during the intervention when they experienced UTI symptoms, including dysuria, urinary frequency or urgency, fever, suprapubic pain, or macroscopic haematuria, they returned for an unscheduled visit for assessment of UTI status and antibiotic treatment as
15 required. Women unable to return for an unscheduled visit utilised an 'emergency kit' to collect an at home urine sample, dropped the sample off at a local pathology laboratory, filled the antibiotic script and then attended an in-clinic appointment on the next available business day.

[0179] Mid-stream urine samples were collected at baseline, 3 months, 6 months, and
20 unscheduled visits. The samples were used to perform dipstick urinalysis, urine culture, and urinary microbiome analysis (subset of 105 participants). Primary analysis, comparing the incidence of culture-confirmed UTIs at any time during the 6-month intervention period between randomised groups, was performed on the full analysis set (comprising all 145 randomised participants with at least one dose of study treatment and
25 with at least one non-missing post-baseline value for the primary outcome) using a log binomial regression model.

[0180] Results

[0181] UTI outcomes

[0182] The absolute reduction in culture positive UTI incidence with consumption of
30 cranberry was 17% with an incidence of 35% in the placebo group vs. 18% in the cranberry powder group. This resulted in a significant adjusted RR reduction in the cranberry group of 52% (P=0.01) for culture-confirmed UTI compared to the placebo

group (Table 1). *Escherichia coli* was the most frequent uropathogenic species detected for culture-confirmed UTIs and its presence at any time during the 6-month period was reduced in the cranberry powder group compared to the placebo group by 51% (P=0.05).

[0183] Incidence of culture-confirmed urinary frequency or urgency (P<0.01) and any one or more culture-confirmed symptom associated with UTI (P=0.01) were also significantly reduced in the cranberry powder group compared to the placebo group. While incidence of symptomatic suspected UTI and culture-confirmed dysuria were not significantly different between cranberry powder and placebo groups.

[0184] Table 1: UTI-related outcomes over the 6-month study period (Full Analysis Set)

Outcome	Placebo no./total no. (%)	Cranberry fruit product of the invention no./total no. (%)	Unadjusted RR (95% CI) ¹	P- value	Adjusted RR (95% CI) ¹	P- value
Incidence of culture-positive UTI (>10 ⁸ cfu/L, 10 ⁵ cfu/mL) at any time during the 6-month intervention period [primary outcome] ²	25/72 (34.7%)	13/73 (17.8%)	0.51 (0.29, 0.92)	0.03	0.48 (0.26, 0.87)	0.01
Age-squared term included in adjusted model ²					0.46 (0.25, 0.82)	0.01

Outcome	Placebo no./total no. (%)	Cranberry fruit product of the intervention no./total no. (%)	Unadjusted RR (95% CI) ¹	P- value	Adjusted RR (95% CI) ¹	P- value
Incidence of symptomatic suspected ³ UTI at any time during the 6-month intervention period ²	28/72 (38.9%)	20/73 (27.4%)	0.70 (0.44, 1.13)	0.15	0.66 (0.41, 1.05)	0.08
Incidence of culture-positive dysuria at any time during the 6-month intervention period ²	18/72 (25.0%)	12/73 (16.4%)	0.66 (0.34, 1.26)	0.21	0.57 (0.29, 1.11)	0.10
Incidence of culture-positive urinary frequency or urgency at any time during the 6-month intervention period	23/72 (31.9%)	7/73 (9.6%)	0.30 (0.14, 0.66)	<.01	0.29 (0.13, 0.63)	<.01
Incidence of culture-positive fever at any time during the 6-month intervention period ⁴	1/72 (1.4%)	3/73 (4.1%)	-	0.62	-	-

Outcome	Placebo no./total no. (%)	Cranberry fruit product of the intervention no./total no. (%)	Unadjusted RR (95% CI) ¹	P- value	Adjusted RR (95% CI) ¹	P- value
Incidence of culture-positive suprapubic pain at any time during the 6-month intervention period ⁴	8/72 (11.1%)	6/73 (8.2%)	-	0.59	-	-
Incidence of culture-positive macroscopic haematuria at any time during the 6-month intervention period ⁴	2/72 (2.8%)	3/73 (4.1%)	-	1.00	-	-
Incidence of any 1 or more culture-positive symptoms associated with UTI at any time during the 6-month intervention period ²	25/72 (34.7%)	12/73 (16.4%)	0.47 (0.26, 0.87)	0.02	0.42 (0.23, 0.78)	0.01

Outcome	Placebo no./total no. (%)	Cranberry fruit product of the intervention no./total no. (%)	Unadjusted RR (95% CI) ¹	P- value	Adjusted RR (95% CI) ¹	P- value
Presence of <i>Escherichia coli</i> on culture on at any time during the 6-month intervention period ^{2,5,6¶}	20/72 (27.8%)	11/73 (15.1%)	0.54 (0.28, 1.05)	0.07	0.49 (0.24, 1.01)	0.05
CI, confidence interval; HR, Hazard ratio; IRR, Incidence rate ratio; RR, relative risk ¹RR from log binomial regression model. Adjusted RR model included age at baseline, sexual activity, UTI history at baseline (number of UTIs reported in last 12 months) and site. Secondary analysis included addition of age-squared as covariate to allow for a potential non-linear effect of age on UTI risk. ²Due to convergence issues, adjusted treatment effect estimate derived from log Poisson regression model with robust variance. ³Symptomatic suspected UTI was defined as a UTI-symptom-associated unscheduled visit. ⁴Fisher's Exact test conducted due to low event rate. Adjusted analysis not conducted. ⁵Presence of <i>Escherichia coli</i> on culture at baseline also included as an adjustment factor in adjusted analysis. ⁶Results for urine culture outcomes (unimputed) for the full analysis set, with non-UTI-associated detections excluded.						

[0185] Urinary microbiome

[0186] Baseline characteristics of participants included in the microbiome analysis. In total, 240 samples were selected to conduct paired microbiome analysis in this study (210 paired samples, 30 unscheduled) corresponding to 48 participants that received the placebo, and 57 that received the cranberry powder. During the study (between baseline and 6 month timepoint), 17 (35%) participants in the placebo group, and 7 (12%)

5

participants in the cranberry powder group, presented with suspected UTI (based on pathology result + medical investigator assessment. Any potential UTI assessment is considered a UTI) (Fischer’s test, p=0.009).

[0187] Baseline urine microbial community profile of participants

- 5
- [0188] Bacterial genera that were prevalent in the urine samples at baseline include bacteria previously isolated from urine such as Anaerococcus, Corynebacterium, Peptoniphilus and Finegoldia, Fenollaria or vaginal-associated bacteria, including Lactobacillus, Atopobium, Gardnerella, Prevotella, Ezakiella and Streptococcus (Figure 1).
- 10
- [0189] Baseline microbiome characteristics did not differ between cranberry powder and placebo (Table 2). Microbial alpha diversity measures of observed OTUs (richness), Pielou’s evenness and Faith’s phylogenetic diversity did not significantly differ between the groups at baseline (Table 2). Composition of the urine microbiota composition (as determined based on unweighted Unifrac distances and weighted Unifrac distance, which
- 15
- computes sample distance based on presence/absence and relative abundances of bacterial taxa, respectively) were similar between groups (Table 2).

Table 2. P-value of comparison of baseline urine microbiota characteristics between the cranberry fruit product of the invention group and the placebo group.

Total bacterial load	
Bacterial load in urine (16S copies/mL)	0.514
Microbial alpha diversity	
Observed OTUs (richness)	0.887
Pielou’s (evenness)	0.317
Faith’s phylogenetic diversity (diversity)	0.829
Microbiota composition	
Unweighted Unifrac (composition)	0.874
Unweighted Unifrac (dispersion)	0.205
Weighted Unifrac (composition)	0.210

Weighted Unifrac (dispersion)	0.995
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[0190]

[0191] After 6 month of supplementation, the relative abundance of *Gardnerella* was significantly lower in the cranberry fruit product of the invention compared to the placebo group ($p<0.05$) (Table 3). This lower level of *Gardnerella* in the urine of women with history of recurrent UTIs happened in parallel of a reduction of the incidence of culture-positive UTI (relative risk reduction of 52%, $p<0.05$) and reduction of the presence of E. coli on culture (relative risk reduction of 51%, $p=0.05$) with the cranberry powder compared to placebo during the 6-month intervention period. These results are in accordance with previous literature demonstrating in animal models that exposure to *Gardnerella* increased the susceptibility of developing UTIs caused by pathogenic E. Coli. Therefore, the lower levels of *Gardnerella* observed at 6 months with the cranberry fruit product of the invention can be considered beneficial.

Table 3. Relative abundance of *Gardnerella* in the urine of participants at baseline and after 6 months of supplementation with placebo or cranberry fruit product.

		Placebo (n=47)	Cranberry Fruit product of the invention (n=57)
Baseline	Mean	0.091	0.072
	SEM	0.026	0.027
	Median	0.000	0.000
	Q1; Q3	0.000; 0.051	0.000; 0.034
	Min; Max	0.000; 0.711	0.000; 0.917
6 months	Mean	0.112	0.081*
	SEM	0.029	0.027
	Median	0.002	0.000

	Q1; Q3	0.000; 0.108	0.000; 0.012
	Min; Max	0.000; 0.792	0.000; 0.865

* $p < 0.05$ vs placebo

CLAIMS

1. A cranberry fruit product for use in a method for reducing and/or inhibiting the growth of microorganisms of the genus *Gardnerella* in the urinary tract of a human or animal subject.
- 5 2. A method of decreasing the population of *Gardnerella* in the urinary tract of a subject, the method comprising administering to a human or animal subject an effective amount of a cranberry fruit product.
3. A cranberry fruit product for use in the prevention or treatment of urinary tract infections (UTI) caused by the growth of microorganisms of the genus
10 *Gardnerella* affecting a human or animal subject.
4. A cranberry fruit product for use in delaying the occurrence of urinary tract infections (UTI) caused by the growth of microorganisms of the genus *Gardnerella* affecting a human or animal subject.
5. A cranberry fruit product for use according to claim 4, wherein the delay in the
15 occurrence of UTI is of at least 3 months, at least 4 months, least 5 months' least 6 months, least 7 months, or more months between UTIs.
6. The cranberry fruit product for use according to claim 1, or the method according to claim 2, wherein the treatment results in the prevention of urinary tract infections (UTI).
- 20 7. The cranberry fruit product for use or the method according to any one of the preceding claims, wherein the use or method results in the prevention and/or the treatment of recurrent UTI.
8. The cranberry fruit product for use or the method according to any one of the preceding claims, wherein the treatment results in the reduction of UTI
25 symptoms such as urgency and frequency.
9. The cranberry fruit product for use or the method according to any one of the preceding claims, wherein the subject is experiencing or is at risk of experiencing UTI.
10. A non-therapeutic method of decreasing the population of *Gardnerella* in the
30 urinary tract of a human or animal subject, the method comprising administering to the subject an effective amount of a cranberry fruit product.
11. A non-therapeutic method according to claim 10, wherein the subject is experiencing or is at risk of experiencing UTI.

12. The composition for use, the method, or the non-therapeutic method according to any one of the preceding claims, wherein the treatment results in the inhibition of the activation and / or growth of *Escherichia coli* in the bladder of the subject.
13. The composition for use, the method, or the non-therapeutic method according to any one of the preceding claims, wherein the cranberry fruit product is selected from one or more of a cranberry juice, a cranberry puree, a cranberry pomace, a dried cranberry powder, whole cranberry powder and/or a cranberry extract.
14. The composition for use, the method, or the non-therapeutic method according to any one of the preceding claims, wherein the cranberry fruit product is enriched with cranberry seeds or cranberry seed meal.
15. The composition for use, the method, or the non-therapeutic method according to claim 14, wherein the seeds or seed meal concentration is of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the total cranberry fruit product.
16. The composition for use, the method, or the non-therapeutic method according to claim 14, wherein the cranberry fruit product is a dried cranberry powder enriched with cranberry seeds or cranberry seed meal.
17. The composition for use, the method, or the non-therapeutic method according to claim 16, wherein the seeds or seed meal concentration is of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the dried cranberry powder, such as from 5% to 35%, such as 15% to 25 % by weight of the dried cranberry powder.
18. The composition for use, the method, or the non-therapeutic method according to claim 14, wherein the cranberry product is a dried cranberry powder obtained from cranberry juice and/or a cranberry pomace and/or a cranberry puree and/or whole cranberry fruits and is enriched with cranberry seeds or cranberry seed meal.
19. The composition for use, the method, or the non-therapeutic method according to claim 18, wherein the seeds or seed meal concentration is of 5%, 10%, 15%, 20%, 25%, 30% or 35% or more by weight of the cranberry powder, such as from 5% to 35%, such as 15% to 25 % by weight of the cranberry powder.

20. The cranberry fruit product for use, the method, or the non-therapeutic method according to any one of the preceding claims, wherein the cranberry fruit product comprises more than 0.3% (w/w) proanthocyanidins according to the BL-DMAC assay or more than 1.5% (w/w) proanthocyanidins according to HPLC.
21. The cranberry fruit product for use, the method, or the non-therapeutic method according to any one of the preceding claims, wherein the cranberry fruit product comprises total phenolic from about 10% to about 60%, such as from about 20% to about 30% wt/wt.
22. The cranberry fruit product for use, the method, or the non-therapeutic method according to any one of the preceding claims, wherein the cranberry fruit product is provided to a human or animal subject in need thereof at a dose of from about 0.017 mg/kg of body weight (bw)/day to 83.33 mg/kg of bw/day, such as from about 3.33 mg/kg of bw/day to 16.67 mg/kg of bw/day, such as 8.33 mg/kg of bw/day.
23. The cranberry fruit product for use, the method, or the non-therapeutic method according to any one of the preceding claims, wherein the subject is a mammal, specially a human, a canine or a feline
24. A method for determining whether a human or animal subject is likely to develop an UTI or a recurrent UTI, wherein the method comprises:
- a) determining the abundance of *Gardnerella* in a urine sample of the subject
 - b) comparing the abundance of *Gardnerella* in at least a first control sample or population of control samples,
 - c) where the abundance of *Gardnerella* of the sample obtained from the subject is substantially similar to or higher than the abundance of *Gardnerella* in at least a first control sample or population of control samples, the subject is considered likely develop UTI, optionally wherein where the abundance of *Gardnerella* of the sample obtained from the subject is at least 5% greater, such as at least 10% greater, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, at least 100% greater, such as at least 200% greater than the abundance of *Gardnerella* in at least a first control sample or population of control samples, the subject is considered to be likely to develop an UTI or a recurrent UTI.