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(54) Title: METHODS AND COMPOSITIONS FOR TREATING AND PREVENTING URINARY TRACT INFECTIONS

(57) Abstract: Described herein are compositions and methods of alleviating, preventing, reducing, suppressing, and/or treating a bacterial infection in a human or non-human animal. The compositions and methods are useful in supporting, for example, genitourinary tract. The methods may include administering to a human or animal in need thereof an effective amount of a composition comprising a cranberry component and a saponin component.

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METHODS AND COMPOSITIONS FOR TREATING AND PREVENTING URINARY TRACT INFECTIONS

BACKGROUND

5 **[0001]** 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 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
10 enterobacteria). Women are at greater risk of developing a UTI than are men.

[0002] Lower urinary tract symptoms (LUTS) become increasingly bothersome as men age, with a prevalence of moderate-to-severe symptoms rising to nearly 50% of men in their eighties. The term LUTS cover both gender but is more often applied to men. LUTS may or may not be related to benign prostatic hyperplasia (BPH), a histological condition characterized by the non-
15 malignant overgrowth of prostatic tissue surrounding the urethra that occurs in 50% of men in their fifties and 90% of men in their eighties. LUTS can also arise from age-related bladder detrusor dysfunction and other sympathetic conditions. LUTS are further classified as voiding or storage symptoms and defined by the international prostate symptoms score (IPSS), a validated tool, widely used among the medical and scientific community.

20 **[0003]** Voiding symptoms include urinary hesitancy, delay in initiating micturition, intermittency, involuntary interruption of voiding, weak urinary stream, straining to void, a sensation of incomplete emptying, terminal dribbling, and may be caused by prostate enlargement or tissue inflammation. Storage symptoms can include urinary frequency, nocturia, urgency, incontinence and bladder pain or dysuria, and may be caused by bladder detrusor
25 overactivity. Overactive bladder (OAB) is a condition more related with women where there is a frequent feeling of needing to urinate to a degree that it negatively affects a person's life.

[0004] Although LUTS and LUTS due to BPH are not a life-threatening condition, the impact of LUTS on quality-of-life (QoL) can be significant and treatment is necessary in most cases to avoid complications. Risk factors include age, prostatic volume and peak urinary flow rate as
30 well as lifestyle, dietary pattern, alcohol consumption, physical activity or genetic factors. Upon diagnosis, watchful waiting is recommended in approximately 34% of cases in the United States. Registered pharmacological treatments for UTI, LUTS and OAB may be responsible for a variety of side effects, thus necessitating development of new treatments.

SUMMARY

[0005] The present invention relates to a composition (or composition of the disclosure) comprising a cranberry component and a saponin component, which is useful for the prevention or treatment of urinary tract infections, and in particular for the preventive treatment of urinary tract infections or treatment against the recurrence thereof. The invention also relates to a process for preparing such composition, to food, nutraceutical or pharmaceutical compositions comprising said composition, and to use thereof in the treatment, alleviating or prevention of urinary tract infections, LUTS, OAB and other urinary tract complications and diseases.

[0006] The present disclosure is also based, in part, on the surprising discovery that lower urinary tract symptoms can be treated by administering a cranberry-based and saponin based composition.

[0007] The present disclosure is also based, in part, on the surprising discovery that lower urinary tract symptoms can be treated by administering a cranberry-based composition in combination with saponin based composition that modulates the microbiome.

[0008] The cranberry and the saponin components can help modulate the urinary and gut microbiome to prevent or help lower urinary tract symptoms or eradicate infections by promoting the restoration of a healthy flora.

[0009] In one aspect, it is provided a composition (or composition of the disclosure) comprising a cranberry component and a saponin component.

[0010] In one aspect, it is provided a method for treatment of urinary tract infections, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder inflammation, prostate inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse, and in particular for the preventive treatment of urinary tract infections, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder inflammation, prostate inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse, or treatment against the recurrence thereof in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition (or composition of the disclosure) comprising a cranberry component and a saponin component.

[0011] In another aspect, is provided a method for supporting genitourinary tract health in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition comprising a cranberry component and a saponin component.

5 **[0012]** As used herein, the term “supporting genitourinary tract” refers to improving or preventing in a subject any problem related to the genitourinary tract such as urinary tract infection, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder inflammation, prostate inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse.

10 **[0013]** In one aspect, is provided the use of a composition comprising a cranberry component and a saponin component in the manufacture of a medicament for use in method for preventing, treating or alleviating an urinary tract infection, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder inflammation, prostate inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse.

15 **[0014]** In one aspect, it is provided a method for modulating or adjusting urinary and/or gut microbiota and/or reverting urinary tract and/or gut microbiome dysbiosis in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition (or composition of the disclosure) comprising a cranberry component and a saponin component.

20 **[0015]** In one aspect, is provided the use of a composition comprising a cranberry component and a saponin component in the manufacture of a medicament for use in method for modulating or adjusting urinary tract and/or gut microbiota and/or reverting urinary tract and/or gut microbiome dysbiosis.

25 **[0016]** In another aspect, is provided a method modulating or adjusting urinary tract and/or gut microbiota and/or reverting urinary tract and/or gut microbiome dysbiosis in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition comprising a cranberry component and a saponin component and wherein.

[0017] The composition of the present disclosure can affect the human or animal genito-urinary microbiome or gut microbiome offering treatment lower urinary tract symptoms or for urinary tract infections.

[0018] The composition of the present disclosure can affect the human or animal vaginal microbiome offering treatment for yeast infections, bacterial vaginosis and pelvic organ prolapse.

[0019] The composition of the present disclosure can affect the human or animal urinary microbiome offering treatment for interstitial cystitis, prostatitis and pelvic organ prolapse.

[0020] The composition of the present disclosure can affect the human or animal urinary and kidney microbiome offering treatment for urolithiasis and hyperoxaluria.

[0021] In some embodiments the animal is an alpaca, bison, cat, cow, chicken, dog, donkey, duck, fish, goat, horse, pheasant, pig, rabbit, sheep or turkey.

[0022] In some embodiments, the cranberry component comprises cranberry powder or cranberry extract.

[0023] The composition further comprises a saponin component. Without limitation, and only by way of illustration, the saponin component included in the composition may comprise a quillaja saponin.

[0024] In some embodiments, the infection is genitourinary infection.

[0025] In some embodiments, the infection is caused by antimicrobial sensitive bacteria.

[0026] In some embodiments, the infection is caused by antimicrobial resistant bacteria.

[0027] In some embodiments, the method does not comprise administering an antimicrobial agent to the human or animal.

[0028] In some embodiments, the method comprises combining the composition with an antimicrobial agent and administering to the human or animal.

[0029] In some embodiments, the method comprises combining the composition with a probiotic and administering to the human or animal.

[0030] 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).

[0031] In some embodiments, the composition further comprises a non-steroidal anti-inflammatory agent.

[0032] In some embodiments, the non-steroidal anti-inflammatory agent is ibuprofen.

[0033] In some embodiments, the composition further comprises a probiotic agent.

[0034] In some embodiments, the composition further comprises an antimicrobial agent.

[0035] In some embodiments, the composition does not comprise an antimicrobial agent.

5 **[0036]** In some embodiments, the composition further comprises an animal feed growth agent.

[0037] 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, quinolones, fluoroquinolones, aminocoumarins, lipamycins, sulfonamides, nitrofurantoin, nitrimidazole, aminoglycosides, tetracyclines, 10 oxazolidinones, macrolides, thiopeptides, chloramphenicol, fusidic acid, clindamycin, lincosamides, glycylcyclines and beta-lactamase inhibitors.

[0038] In some embodiments, the probiotic agent is selected from the group consisting of *Bacillus coagulans*, *Akkermansia muciniphila*, *Lactobacillus gasseri*, *Bifidobacterium bifidum*, 15 *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 protectis*, *Lactobacillus iners*, *Lactobacillus jensenii*, *Lactobacillus fermentum*, *Lactobacillus brevis*, *Lactobacillus casei*, 20 *Lactobacillus vaginalis*, *Lactobacillus delbrueckii*, and *Lactobacillus salivarius*.

[0039] In some embodiments, the infection-causing bacterial strain is gram positive or gram negative.

[0040] In some embodiments, the composition is a liquid, gel, tablet, a capsule, a sachet, a powder, a gum, an ointment, syrup, a suppository, a patch, a softgel, a tampon, a wound 25 dressing, a wound rinse, a soap, or a lotion.

[0041] In another aspect, the invention provides a therapeutic composition formulated for use in the methods described herein.

[0042] In some embodiments, the therapeutic composition is formulated for oral administration.

DETAILED DESCRIPTION

[0043] The present disclosure is related to a composition (or composition of the invention) comprising a cranberry component and a saponin component

[0044] The cranberry component used in the present disclosure may be a cranberry juice, a cranberry puree, a cranberry powder, a cranberry extract or a combination thereof. In one embodiment, the cranberry powder is obtained from whole cranberry fruit.

[0045] The cranberry component may be in the form of a liquid or in the form of a powder.

[0046] In one embodiment, the cranberry is *Vaccinium macrocarpon*. In some embodiments, the cranberry is *Vaccinium microcarpon*. In some embodiments, the cranberry is *Vaccinium oxycoccus*.

[0047] In one embodiment, the cranberry component 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.

[0048] The term “aqueous extract” as used herein, refers to the extract obtained from cranberry when the extraction from the plant has been performed using water as the only solvent.

[0049] The term “alcohol extract” as used herein, refers to the extract obtained from cranberries when the extraction from the plant 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.

[0050] 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.

[0051] In one embodiment, the cranberry component may be an aqueous extract of cranberry. In another embodiment the cranberry component may be a purified cranberry extract. In one
5 embodiment, the cranberry component has from about 1% to 30% proanthocyanidins, such as from about 3% to about 20%, or such as from about 3% to 15%, or 5% to 10% wt/wt. In one embodiment, the total phenolic of the cranberry component is from about 10% to about 60%, such as from about 20% to about 30% wt/wt.

[0052] In another aspect, the invention provides therapeutic composition comprising dried
10 cranberry powder.

[0053] In one embodiment, the cranberry component (such as a cranberry juice, a cranberry
puree, a dried cranberry powder, whole cranberry powder or a cranberry extract) 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
15 component. In one embodiment, the seeds or seed meal concentration may be from 5% to 35%
by weight of cranberry component, such as from 10% to 25%, such as 20% of seeds or seed meal
by weight of cranberry component. In one embodiment, the cranberry component may be a
cranberry extract enriched in cranberry seeds or seed meal. The seeds or seed meal concentration
may be of 5%, 10%, 15%, 20%, 25, 30% or 35% or more by weight of cranberry component. In
20 one embodiment, the seeds or seed meal concentration may be from 5% to 35% by weight of
cranberry component, such as from 10% to 25%, such as 20% of seeds or seed meal by weight of
cranberry component. In one embodiment, the cranberry component may be a cranberry extract
enriched with about 20% cranberry seed or seed meal. In another embodiment, the cranberry
component comprises dried cranberry powder (such as a dried cranberry powder from the whole
25 cranberry fruit) and dried cranberry seeds or seeds meal. The seeds or seed meal concentration
may be of 5%, 10%, 15%, 20%, 25, 30% or 35% or more by weight of whole cranberry fruit
powder. In one embodiment, the seeds or seed meal concentration may be from 5% to 35% by
weight of whole cranberry fruit powder, such as from 10% to 25%, such as 20% of seeds or seed
meal by weight of whole cranberry fruit powder. In one embodiment, the cranberry component
30 may be a dried cranberry powder enriched with about 20% cranberry seed or seed meal by
weight of dried cranberry powder.

[0054] In some embodiments, the composition 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

[0055] In some embodiments, the composition comprises less than about 15% of sugars by weight, such as less than 12% or less than 10 % of sugars by weight.

5 **[0056]** In some embodiments, the composition comprises from about 1 % to about 5% of quinic acid by weight. According to certain illustrative embodiments, the composition comprises from about 2.2% to about 3.2% of quinic acid by weight.

[0057] In some embodiments, the composition comprises from about 0.4% to about 4% of malic acid by weight.

10 **[0058]** In some embodiments, the composition comprises from about 1 % to about 5% of citric acid by weight. According to certain illustrative embodiments, the composition comprises from about 1.8% to about 3.2% of citric acid by weight.

[0059] In some embodiments, the composition 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 % 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-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.

[0060] In some embodiments, the composition 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 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% 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.

[0061] In some embodiments, the composition 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% 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.

5 **[0062]** In some embodiments, the composition 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.

[0063] In some embodiments, the composition comprises about 51 µg lariciresinol, about 12 µg secoisolariciresinol or about 78 µg/ pinoresinol per 100g of the composition by weight.

10 **[0064]** The saponin component may be of natural (obtained or obtainable form a natural source rich in saponins) or of synthetic origin. The saponin component used in the present invention may be selected from one or more of quillaja saponins, tea saponins, licorice saponins, beet root saponins, sugar beet saponins, ginseng saponins, glycyrrhizin, oat bran saponins, yucca saponins and mixtures thereof. In one embodiment the saponin is quillaja saponin(s). In one embodiment the saponin component is a natural extract, such as a quillaja extract, tea extract, licorice extract, 15 beet root extract, sugar beet extract, ginseng extract, oat extract, yucca extract or a mixture thereof, with at least 5% wt/wt, or at least 10% wt/wt , or at least 15% wt/wt, or at least 20% wt/wt, or at least 25% wt/wt, or at least 30% wt/wt, or at least 35% wt/wt, or at least 40% wt/wt, or at least 50% wt/wt, or at least 60% wt/wt, or at least 70% wt/wt, or at least 80% wt/wt, or at least 95% wt/wt of saponins. In one embodiment the saponin component may be a quillaja 20 extract with at least 60% saponins, such as 65% wt/wt of saponins.

[0065] The present disclosure is also related to a method for preventing, treating or alleviating an urinary tract infection, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder 25 inflammation, prostate inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse, in a human or animal in need thereof, the method comprising administering to the patient an effective amount of a composition comprising a cranberry component and a saponin component.

30 **[0066]** The present disclosure is also related to a composition comprising a cranberry component and a saponin component for use in preventing, treating or alleviating an urinary tract infection, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder inflammation, prostate

inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse. In one embodiment the patient is a human or animal in the need thereof.

[0067] The present disclosure is also related to the use of a composition comprising a cranberry component and a saponin component in the preparation of a medicament or nutraceutical for preventing, treating or alleviating an urinary tract infection, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder inflammation, prostate inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse. In one embodiment the patient is a human or animal in the need thereof.

[0068] In another aspect, is provided a method for supporting genitourinary tract health in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition comprising a cranberry component and a saponin component.

[0069] In some embodiments, the composition of the present disclosure can be used for treating urinary tract infections (UTIs) by itself. In some embodiments, the cranberry component can be used for treating urinary tract infections (UTIs) in combination with a NSAID.

[0070] In one aspect, it is provided a method for modulating or adjusting urinary tract and/or gut microbiota and/or reverting urinary tract and/or gut microbiome dysbiosis in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition (or composition of the disclosure) comprising a cranberry component and a saponin component.

[0071] In one aspect, is provided the use of a composition comprising a cranberry component and a saponin component in the manufacture of a medicament for use in method for modulating or adjusting urinary tract and/or gut microbiota and/or reverting urinary tract and/or gut microbiome dysbiosis.

[0072] In another aspect, is provided a method modulating or adjusting urinary tract and/or gut microbiota and/or reverting urinary tract and/or gut microbiome dysbiosis in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition comprising a cranberry component and a saponin component and wherein.

[0073] In one embodiment, the modulated or adjusted urinary tract and/or gut microbiota and/or reverted urinary tract and/or gut microbiome dysbiosis is selected from the group

consisting of *Dialister*, *Weeksella*, *Subdoligranulum*, *Fusicatenibacter*, *Leucobacter*, *Porphyromonas*, *Corynebacterium*, *Oligella*, *Sneathia*, *Prevotella_9*, *Blautia*, *Klebsiella*, *Bacteroides*, *Prevotella*, *Acinetobacter*, *Citrobacter*, *Faecalibacterium*, *Streptococcus*, *Lactobacillus*, *Escherichia*, and combinations thereof.

5 **[0074]** In one embodiment, the modulated or adjusted urinary tract and/or gut microbiota and/or reverted urinary tract and/or gut microbiome dysbiosis is *Escherichia*. In an embodiment, *Escherichia* abundance is decreased in the urinary tract.

10 **[0075]** Dysbiosis is often defined as an “imbalance” in for example the urinary or gut 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.

[0076] As shown in Figures 1 and 2, the treatment with the composition of the present invention leads to an increase in microbiome diversity. Therefore, in an embodiment, microbiome diversity is increased, in particular the urine and/or gut microbiome diversity.

15 **[0077]** In another aspect is provided a therapeutic composition, pharmaceutical composition or a nutraceutical composition comprising the composition of the invention (composition comprising a cranberry component and a saponin component) for use in the methods of treatment or uses described herein. In one preferred embodiment, the therapeutic composition or nutraceutical composition is formulated for oral administration.

20 **[0078]** In another aspect, is provided a pharmaceutical composition, a nutraceutical composition or a food composition comprising the composition of the invention and optionally a physiologically acceptable excipient and/or carrier.

25 **[0079]** In some embodiments, the composition of the present disclosure, the pharmaceutical composition, the nutraceutical composition or the food composition is provided in the form of a liquid, gel, tablet, a capsule, a sachet, a powder, a gum, an ointment, syrup, a suppository, a patch, a softgel, a tampon, a wound dressing, a wound rinse, a soap, or a lotion.

[0080] In some embodiments, the composition of the present disclosure, the pharmaceutical composition or the nutraceutical composition is suitable for oral, rectal, intravenous, intravesical or vaginal delivery.

30 **[0081]** In some embodiments, the composition of the present disclosure, the pharmaceutical composition or the nutraceutical composition comprises an enteric coating.

[0082] In some embodiments, the composition of the present disclosure, the pharmaceutical composition or the nutraceutical composition may be used in combination with probiotics.

[0083] In some embodiments, the composition of the present disclosure, the pharmaceutical composition or the nutraceutical composition may be used in combination with an anti-inflammatory agent.

[0084] In some embodiments, the composition of the present disclosure, the pharmaceutical composition or the nutraceutical composition may be used in combination with an antimicrobial agent.

[0085] 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.

[0086] In some embodiments, the composition of the present disclosure is used in prophylaxis to avoid the need for antimicrobial treatment, sparing the healthy microbiome.

[0087] In some embodiments, a solid oral dosage comprising the composition described herein is a tablet, a capsule, or a softgel. In some embodiments, such solid oral dosage comprises from 50 mg to 1500 mg of the therapeutic composition, 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.

[0088] In one embodiment, the ratio of the cranberry component to the saponin component (such as quillaja saponin) in the composition is from 10:0.1 to 1:10, such as 10:0.1, 10:0.2, 10:0.3, 10:0.4, 10:0.5, 10:0.6, 10:0.7, 10:0.8, 10:0.9, 10:1, 10:1.1, 10:1.2, 10:1.3, 10:1.4, 10:1.5, 10:1.6, 10:1.7, 10:1.8, 10:1.9, 10:2, 10:3, 10:4, 10:4, 10:6, 10:7, 10:8, 10:9, 10:10, 9:10, 8:10, 7:10, 6:10, 5:10, 4:10, 3:10, 2:10 or 1:10. In one embodiment, the ratio is from 10:0.5 to 10:2, such as 10:0.7, 10:1, 10:1.1 or 10:1.5.

[0089] 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.

[0090] 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 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 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
5 Pharmaceutical Sciences 1447-1676 (Alfonso R. Gennaro eds., 19th ed. 1995).

[0091] In some embodiments, a 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,
10 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
15 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
20 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
25 pharmaceutical grade.

[0092] 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
30 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.

[0093] 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.

[0094] 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.

[0095] 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. 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.

[0096] In some embodiments, a controlled or sustained release composition comprises a minimal amount of a therapeutic composition to alleviate the symptoms of, treat or prevent lower urinary tract symptoms (LUTS), urinary tract infections (UTIs), pelvic organ prolapse (POP), urolithiasis or hyperoxaluria, benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, bladder obstruction, interstitial cystitis, overactive bladder (OAB), underactive bladder, prostatitis, bladder and prostate inflammation, prostate fibrosis or pelvic pain in a patient over a period of time. Advantages of controlled or sustained release compositions include extended activity of the drug, reduced dosage frequency, and increased

subject compliance. In addition, controlled or sustained release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels active ingredients present in the therapeutic composition, and can thus reduce the occurrence of adverse side effects.

5 **[0097]** 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
10 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
15 temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

[0098] The amount of the composition of the present disclosure (comprising a cranberry component and a saponin), the pharmaceutical composition or the nutraceutical composition that is useful for treating any of the diseases and symptoms described before (such as LUTS, OAB,
20 etc) 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,
25 however, range from about 1 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
30 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.

5 **[0099]** The compositions described herein can be administered as long as the symptoms persist or longer. In some embodiments, the therapeutic composition is administered for 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days.

10 **[0100]** 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.

[0101] 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.

15 **[0102]** The compositions described herein can be assayed in vitro or in vivo for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

20 **[0103]** As used herein, the recitation of a numerical range for a variable is intended to convey that the invention may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value within the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value within the numerical range, including the end-points of the range. As an example, and without limitation, a variable which is described as having values between 0 and 2 can take the values 0, 1 or 2 if the variable is inherently discrete, and can take the values 0.0, 0.1, 0.01, 0.001, or any other real values ≥ 0 and ≤ 2 if the variable is inherently continuous.

25 **[0104]** As used herein, the term “treatment” or grammatical equivalents encompasses the improvement and/or reversal of the symptoms of disease (e.g. LUTS). The term “treatment” refers to both therapeutic treatment and prophylactic or preventative measures. For example, those who may benefit from treatment with compositions, uses and methods of the present invention include those already with a disease and/or disorder (e.g., elevated cholesterol levels) as well as those in which a disease and/or disorder is to be prevented (e.g., using a prophylactic treatment of the present invention).

[0105] The term “prevention” in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be at risk or predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

[0106] As used herein, the term “at risk for disease” refers to a subject (e.g., a human) 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 invention be limited to any particular disease.

[0107] A therapeutically effective amount of any embodiment of the present invention is determined using methods known to pharmacologists and clinicians having ordinary skill in the art. For example, an effective amount can be determined subjectively by administering increasing amounts of the compositions of the present invention until such time the patient being treated shows reduction in LUTS symptoms for example using the Urinary Tract Infection Symptoms Assessment Questionnaire (UTISA) as described in the experiments of the present invention,

[0108] As used herein, unless specifically indicated otherwise, the word "or" is used in the inclusive sense of "and/or" and not the exclusive sense of "either/or."

[0109] As used herein, "about" means within $\pm 10\%$. For example, "about 1" means "0.9 to 1.1", "about 2%" means "1.8% to 2.2%", "about 2% to 3%" means "1.8% to 3.3%", and "about 3% to about 4%" means "2.7% to 4.4%."

[0110] The patent and scientific literature referred to herein establishes knowledge that is available to those of skill in the art. The issued U.S. patents, allowed applications, published foreign applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference.

[0111] While a number of embodiments of the invention have been described, it is apparent that the basic examples may be altered to provide other embodiments that utilize the compositions, methods, and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example herein.

EXAMPLES

[0112] Example 1. Clinical trial with a composition of Cranberry and quillaja.**[0113]** Cranberry and quillaja composition

[0114] The cranberry component is a dried cranberry powder that is enriched in 20% of
 5 cranberry seeds or seed meal by dry weight.

[0115] The quillaja component is an extract powder containing approximately 65% saponins by
 dry weight.

[0116] 1. Study design:

Sample Size: N= 38 participants

Enrollment: This study has enrolled 38 subjects.

Study Population: Healthy pre-menopausal women 18 years or older with a
 symptomatic uncomplicated UTI.

Enrollment Period: 3 months

Study Design: Open label study design to test the effect of cranberry and quillaja
 15 on symptoms of UTI and the urinary and gut microbiome before
 and after antibiotic therapy.

Site Enrolling

Participants: St. Joseph's Hospital – London, Ontario

Participant Duration: 14 to 18 days

Study Product

Description: Cranberry (450 mg) and quillaja (50 mg) capsules taken orally
 twice daily (morning and evening) for a total daily dose of 900 mg
 cranberry and 100 mg quillaja for 14 days. Nitrofurantoin 100 mg
 taken orally twice daily for five days as a rescue medication if
 25 symptoms do not subside.

Primary Objectives: To study the effect of cranberry and quillaja on UTI symptoms in
 women with uncomplicated Urinary Tract Infection (UTI).

Secondary Objectives: To study the modulation of the urinary and gut microbiome pre
 and post-antibiotic use.

Primary Endpoints: 1) Time to symptom resolution is be determined using the Urinary
 Tract Infection Symptoms Assessment Questionnaire (UTISA), see
 tables 1 and 2. It assesses the degree of symptoms and bother on a
 scale of 0 to 3, and has 3 domains of urinary regularity, problems
 with urination and pain associated with urination. The fourth
 35 domain includes the presence of hematuria. Subjects complete
 UTISA every day for 14 days.

2) Time to UTI antibiotic initiation is assessed using study forms. Subjects have access to a clinically prescribed UTI antibiotic, nitrofurantoin. Subjects are asked to record each day their intake of any antibiotic during the study period.

- 5 Secondary Endpoints: Urinary and gut microbiome factors: magnitude of initial dysbiosis, changes prior to antibiotic initiation if applicable, changes after antibiotic initiation, time to microbiome stability.

[0117] 2. Subject Selection

[0118] 2.1 Study Population

- 10 **[0119]** Subjects seeking care for symptoms suggestive of acute UTI who meet the inclusion and exclusion criteria will be eligible for participation in this study.

[0120] 2.2 Inclusion Criteria

1. Pre-menopausal women 18 years and over
2. Presenting with typical symptoms of an uncomplicated UTI
- 15 3. Positive leukocyte or nitrite on in-office urine dipstick confirmed
4. Able to swallow capsules
5. Willing and able to fill out/ answer questionnaires and comply with the study requirement
6. Willing to initiate clinically prescribed antibiotic therapy (typically 5-day antibiotic).
- 20 7. Provided written informed consent
8. BMI >17.5kg m² and <35kg m²

[0121] 2.3 Exclusion Criteria

1. Regular use of Vaccinium containing products (e.g. all forms of blueberries, cranberries, bilberry, lingonberry etc. i.e. fruit, dried fruit, pills, juices or supplements) within 28 days of
- 25 Day 1.
2. Allergy to cranberry, tree bark, or quillaja.
3. Use of any antibacterial supplements or products, that in the opinion of the Medical Investigator may interfere with the study outcomes, within 28 days of Day 1.
4. A history of >5 UTIs in the last 6 months (confirmed by self-report or health
- 30 professional).
5. Use of antibiotics or antibiotics for prophylaxis to treat a UTI within 28 days of Day 1.
6. Women of child bearing potential not willing to use adequate and effective methods of contraception throughout the study, in the opinion of the Investigator.

7. Positive urine dipstick pregnancy test at screening on Day 1, currently pregnant and/or breastfeeding.
8. History of an adverse reaction or known hypersensitivity or suspected allergy to the investigational product ingredients.
- 5 9. History of pyelonephritis or reflux.
- 10 10. Presence of an intermittent or indwelling urinary catheter.
11. Anatomical abnormalities of the urinary tract (self-reported).
12. History of or known clinically significant renal or urological disease (self-reported), at the discretion of the investigator.
13. History of or known clinically significant cardiac disease, at the discretion of the investigator.
14. History of or known clinically significant liver disease, at the discretion of the investigator.
- 15 15. History of or known clinically significant gastrointestinal disease, at the discretion of the investigator.
16. History of or known metabolic disorder or diabetes.
17. History of or known incomplete emptying of bladder.
18. History or presence of alcohol or illicit drug abuse, any surgical history, clinical condition or organ dysfunction that in the opinion of the Investigator may affect the participant's ability to participate in the study or the study results.
- 20 19. Currently hospitalized or any planned hospitalizations within the study period.
20. Immunocompromised participants or participants receiving immunosuppressive medication
21. Currently taking warfarin or has received Warfarin within 28 days of Day 1.
- 25 22. Received an investigational drug within 28 days of Day 1 (pills, juices or supplements).

[0122] 2.4 Screen Failures

[0123] Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

[0124] 2.5 Strategies for Recruitment and Retention

Subjects are recruited for the study from St. Joseph's Hospital in London, ON.

Subjects are recruited based on the Inclusion and Exclusion criteria listed in Section 2.2 and 2.3, respectively.

[0125] 3. Study Procedures

5 Subjects have two in-office visits. At Visit 1, the subjects are required to provide a urine sample to test for leukocyte or nitrites, perform a urine culture and a pregnancy test. Subjects are also asked to provide a stool sample if possible. Recognizing that providing a stool sample at Visit 1 may not be possible, the subject take a stool sample at home and identify this as Day 1. After taking the stool sample the subjects begin taking the product substance
10 immediately and then again that evening even if the first dose is taken in the afternoon and not the morning. The subjects shall then take the remaining product in the morning and evening as instructed until all 28 doses are gone and collect urine each day for 14 days and a second stool sample on Day 14 before returning for Visit 2.

[0126] 3.1. Sample Collection and Shipping to Laboratory for Analysis

[0127] Urine sample collection

[0128] Urine sample are collected at Visits 1, every day after Visit 1, and at Visit 2. Urine will be collected using Peezy and AssayAssure™ urine collection kits. Each subject is asked to wash their hands with soap and water and collect midstream urine.

[0129] Peezy midstream urine collection device (Forte Medical, London, UK) allows the
20 collection of approximately 30 mL of urine into a sterile container. It has been reported to allow the collection of urine that is significantly less contaminated with bacteria that was distinct from the periurethra compared to the standard clean catch method.

[0130] AssayAssure™ (Sierra Molecular Corp, Princeton, NJ) is a urine sample stabilization system designed to preserve cell viability by slowing cellular metabolism and providing thermal
25 protection for up to 26 days at room temperature. After subjects collect urine using Peezy collection device, the urine is transferred and stored in the AssayAssure transport tubes. The tubes are stored at a refrigerated temperature (2-4°C) and brought into clinic at Visit 2. The priority for the urine specimen on Visit 1 is clinical UTI testing (UA and reflex urine culture). All remaining urine from Visit 1 are saved for microbiome research purposes (sequencing of
30 microbiome). A minimum sample quantity of 20 mL is need for the microbiome testing.

[0131] 4. Study Intervention

[0132] 4.1 Study Intervention

Following baseline assessment, subjects are provided with study product, and instructed to take one 450 mg cranberry capsule, and one 50 mg quillaja capsule in the morning and to repeat the same dose in the evening (Schema 1). The total daily dosage of cranberry will be 900 mg, and the total dosage of quillaja will be 100 mg per day. If UTI symptoms persist before Visit 2, subjects can start nitrofurantoin 100mg PO BID for 5 days that is provided at Visit 1 at any time.

[0133] 4.2 Dosing and Administration

Subjects are instructed to take one 450 mg cranberry capsule, and one 50 mg quillaja capsule in the morning and another in the evening. The total daily dosing will be 900 mg of cranberry, and 100 mg of quillaja per day for 14 days. If a subject is starting in the afternoon, they should take the morning dose at that time and then later take the evening dose. If subjects accidentally skip a dose they can double up on the next dose only if taken on the same day.

[0134] 4.3 Duration of Therapy and Criteria for Removal from Study

[0135] Subjects take cranberry 900mg and quillaja 100mg daily for 14 days until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

[0136] 5. Measurement of Effect

The results of this study are contingent upon subjects' responses to the UTISA questionnaire tables 1 and 2 (Clayson D, Wild D, Doll H, Keating K, Gondek K. Validation of a patient-administered questionnaire to measure the severity and bothersomeness of lower urinary tract symptoms in uncomplicated urinary tract infection (UTI): the UTI Symptom Assessment questionnaire. BJU Int. 2005 Aug;96(3):350-9) and study forms, which provide the efficacy of cranberry and quillaja in alleviating UTI symptoms. These measurements are to be completed by the subjects throughout the study.

[0137] Primary endpoint measures:

The degree of symptoms of UTI is measured based on subject responses recorded on UTISA. Time to UTI antibiotic initiation is assessed using study forms.

Secondary endpoint measure:

Urinary and gut microbiome factors such as the magnitude of initial dysbiosis, changes prior to antibiotic initiation will be measured.

About Your Symptoms and Their Impact on Your Life (for use at visit 1)

Please indicate whether you have had the following symptoms/problems in the past 24 hours and how severe they were: <i>(Please circle one number for each symptom)</i>				SYMPTOMS	If you have experienced these symptoms/problems in the past 24 hours, please indicate <u>how bothersome</u> they were? <i>(Please circle one number for each symptom)</i>			
Did not have	Mild	Moderate	Severe		Not at all	A little	Moderately	A lot
0	1	2	3	Frequency of urination (going to the toilet very often)	0	1	2	3
0	1	2	3	Urgency of urination (a strong and uncontrollable urge to pass urine)	0	1	2	3
0	1	2	3	Pain or burning when passing urine	0	1	2	3
0	1	2	3	Not being able to empty your bladder completely/passing only small amounts of urine	0	1	2	3
0	1	2	3	Pain or uncomfortable pressure in the lower abdomen(pelvic area caused by your urinary tract infection)	0	1	2	3
0	1	2	3	Low back pain caused by your urinary tract infection	0	1	2	3
0	1	2	3	Blood in your urine	0	1	2	3

8. Please give an overall rating of the severity of your urinary tract infection symptoms as they are at this moment (Please circle the number of your answer)

0 No symptoms at all

1 Mild

2 Moderate

3 Severe

Table 1. UTISA questionnaire for use at baseline

About Your Symptoms and Their Impact on Your Life (for use after visit 1)

Since you last completed this questionnaire please indicate whether you have had the following symptoms/problems and how severe they were: <i>(Please circle one number for each symptom)</i>				SYMPTOMS	Since you last completed this questionnaire, if you have experienced these symptoms/problems please indicate <u>how bothersome</u> they were? <i>(Please circle one number for each symptom)</i>			
Did not have	Mild	Moderate	Severe		Not at all	A little	Moderately	A lot
0	1	2	3	Frequency of urination (going to the toilet very often)	0	1	2	3
0	1	2	3	Urgency of urination (a strong and uncontrollable urge to pass urine)	0	1	2	3
0	1	2	3	Pain or burning when passing urine	0	1	2	3
0	1	2	3	Not being able to empty your bladder completely/passing only small amounts of urine	0	1	2	3
0	1	2	3	Pain or uncomfortable pressure in the lower abdomen (pelvic area caused by your urinary tract infection)	0	1	2	3
0	1	2	3	Low back pain caused by your urinary tract infection	0	1	2	3
0	1	2	3	Blood in your urine	0	1	2	3

8. Please give an overall rating of the severity of your urinary tract infection symptoms as they are at this moment *(Please circle the number of your answer)*

0 No symptoms at all 1 Mild 2 Moderate 3 Severe

9. Since your last completed this questionnaire, have there been any changes in your urinary tract infection symptoms? *(Please circle the number of your answer)*

0 about the same 1 better 2 worse

(Note - If the patient responded 1-better) to question 9, go on question 10 below)

10. Please indicate how much better *(circle the number of your answer)*

6 a very great deal better 5 a great deal better 4 a good deal better

3 moderately better 2 somewhat better 1 a little better

Table 2. UTISA questionnaire for use at Day 2-14

(0138) 6. Statistical Considerations.

The Statistical Package for the Social Sciences (SPSS, Chicago, IL) is used to perform all statistical analyses. Statistical significance is set at $P < 0.05$ a priori. Descriptive analyses are used to describe the characteristics of the patient sample (mean, standard deviation, percentages, and frequencies). One-way analysis of variance is used to evaluate the continuous variables, and chi-square tests is used to evaluate the categorical variables.

(0139) Power Calculation and Sample Size.

The probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference pre and post treatment is a reduction of 7.5

symptom units on the UTISA questionnaire. This is based on the assumption that the standard deviation of the response variable is 4.6.

[0140] 7. Analysis of Endpoints

[0141] 7.1 Analysis of Primary Endpoints

5 Primary end point 1) Time to symptom resolution measured by the subject responses on UTISA Statistical analysis.

Primary end point 2) Time to UTI antibiotic initiation is assessed using study forms. Subjects have access to a clinically prescribed UTI antibiotic. Subjects are asked to record each day their intake of any antibiotic during the study period. The nonuse of the rescue antibiotic is
10 considered a successful response.

[0142] 8. Microbial composition data for Urobiome study

[0143] 8.1 Methods:

Urine samples were processed within 6 hours of their collection as previously described (Al and Burton, 2021). Fecal samples were collected on toilet paper and processed as previously
15 described (Al et al., 2018). Microbiota sequencing was performed on an Illumina MiSeq as previously described following PCR amplification of the V4 region of the 16S rRNA gene (Al et al., 2020). Raw reads were demultiplexed using Cutadapt (v3.4)(Martin, 2011) and quality filtered following the DADA2 pipeline (Callahan et al., 2016). The remaining filtered
20 reads were assigned taxonomy to amplicon sequence variants (SVs) using the SILVA (v138) training set (Quast et al., 2013). Downstream analysis was performed with ALDEx2, Vegan, and core R packages (Fernandes et al., 2013; Oksanen et al., 2019; R Core team, 2019).

[0144] 8.2 Results:

The microbiota was characterized for 13 samples from one participant, of which three were fecal and ten were urine per person. The raw reads were stringently filtered for quality: of the
25 initial average yield of 131 729 reads per sample, filtering pruned an average of 13%, such that approximately 117 000 reads per sample were maintained for the downstream analyses. 2541 SVs were initially identified in the samples; a further filtering was performed such that SVs were removed that did not comprise >1% of the relative abundance in any sample, and did not assign to chloroplast, mitochondrial, or eukaryotic DNA. 116 SVs remained and were
30 utilized for downstream analyses.

[0145] When evaluating the microbiota, the fecal microbiota was not significantly altered during the 14 days, as measured by Shannon's index of alpha diversity or Aitchison distance

from the baseline (data not shown). In contrast, although not statistically significant, the relative abundance of the genus *Escherichia* in urine samples appears to decrease by day 14 in comparison to the baseline values on day 1 (Figures 1a/b & 2a/b).

[0146] Figures 1a and 1b show the relative bacterial abundance of all samples. Each vertical bar represents the relative SV abundance within a single sample. Samples are grouped by participant and sample type. Relative abundance of SVs is coloured by genera, with the 20 most abundant genera shown in the legend. Samples are coloured by sample type (fecal samples are gray, urine samples are yellow), and denoted with the day of sample collection. Figure 1a is in color, Figure 1b in grayscale, but they show the same data.

[0147] Figures 2a and 2b show the relative bacterial abundance from baseline, midpoint, and day 14. Each vertical bar represents the relative SV abundance within a single sample. Samples are grouped by participant and sample type. Relative abundance of SVs is coloured by genera, with the 20 most abundant genera shown in the legend. Samples are coloured by sample type (fecal samples are gray, urine samples are yellow), and denoted with the day of sample collection. Figure 2a is in color, Figure 2b in grayscale, but they show the same data.

[0148] Participant 1 urine samples were significantly higher in Shannon's index of alpha diversity with higher variability over time (two-tailed student's t-test, $P = 0.021$; F test of variances, $P = 0.018$), and trended towards higher Beta diversity as measured by Aitchison distance from baseline (two-tailed students t-test, $P = 0.08$ respectively).

[0149] When evaluating the symptoms, using the UTISA questionnaire, participant 1 experienced a noticeable decrease in the severity and bothersome ratings of her symptoms at Day 14 (Table 3):

	Baseline	Day 2	Day 3	Day 4	Day 5	Day 6	Day 11	Day 14
Frequency of urination (going to the toilet very often)	3	1	2	2	1	1	2	0
Urgency of urination (a strong and uncontrollable urge to pass urine)	2	0	1	1	2	0	1	0
Pain or burning when passing urine	1	1	0	0	0	0	2	0
Not being able to empty your bladder completely / passing only small amounts of urine	0	0	0	0	0	0	0	0
Pain or uncomfortable pressure in the lower abdomen / pelvic area caused by your urinary tract infection	1	0		1	0	0	0	0
Low back pain caused by your urinary tract infection	0	0	0	0	0	0	0	0
Blood in your urine	0	0	0	0	0	0	0	0

Total (severity)	7	2	4	4	3	1	5	0
Frequency of urination (going to the toilet very often)	3	1	2	2	1	1	2	0
Urgency of urination (a strong and uncontrollable urge to pass urine)	2	0	1	1	1	0	2	0
Pain or burning when passing urine	2	1	0	0	0	0	1	0
Not being able to empty your bladder completely / passing only small amounts of urine	0	0	0	0	0	0	0	0
Pain or uncomfortable pressure in the lower abdomen / pelvic area caused by your urinary tract infection	1	0	1	1	0	0	0	0
Low back pain caused by your urinary tract infection	0	0	0	0	0	0	0	0
Blood in your urine	0	0	0	0	0	0	0	0
Total (bothersome)	8	2	4	4	2	1	5	0
Please give an overall rating of the severity of your urinary tract infection symptoms as they are at this moment.	2	1	1	1	1	1	2	0
Since you last completed this questionnaire, have there been any changes in your urinary tract infection symptoms		1	1	2	0	1	2	1
Please indicate how much better		3	2					6

Table 3. Results of the UTISA questionnaire for participant 1

[0150] The decrease in *Escherichia* in urine and the increase in microbiome diversity appear concomitantly with the decrease of symptoms at Day 14.

[0151] References:

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R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

WHAT IS CLAIMED IS:

1. A composition comprising a cranberry component and a saponin component.
2. The composition according to claim 1, wherein the cranberry component comprises cranberry powder or cranberry extract.
- 5 3. The composition of claim 1 or 2, wherein the saponin component is quillaja saponin.
4. The composition of any of claims 1 to 3, wherein the cranberry component may be enriched with cranberry seeds, cranberry seeds meal, or a combination thereof.
5. The composition of any of claims 1 to 4, wherein the ratio between the cranberry component and the saponin component is from about 10:0.5 to about 10:2.
- 10 6. The composition of claim 5, wherein the ratio between the cranberry component and the saponin component is selected from the group consisting of from 10:0.7, 10:1, 10:1.1 and 10:1.5.
7. A pharmaceutical composition, a nutraceutical composition or a food composition comprising the combination according to any one of claims 1 to 6 and optionally a physiologically acceptable excipient, a physiologically acceptable carrier, or combinations thereof.
- 15 8. A pharmaceutical composition or a nutraceutical composition according to claim 7 formulated for oral administration.
9. A method for preventing, treating or alleviating an urinary tract infection, lower urinary tract symptoms (LUTS), the symptoms of benign prostatic hyperplasia (BPH), erectile dysfunction (ED), urinary incontinence, overactive bladder (OAB), bladder obstruction, interstitial cystitis, underactive bladder, prostatitis, bladder inflammation, prostate inflammation, prostate fibrosis, pelvic pain, H. pylori infection, urolithiasis, hyperoxaluria and/or pelvic organ prolapse, in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition according to any of claims 1 to 6 or a pharmaceutical composition or nutraceutical composition according to claims 7 or 8.
- 20 10. A method for supporting genitourinary tract health in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition comprising a cranberry component and a saponin component according to any of claims 1 to 6 or a pharmaceutical composition or nutraceutical composition according to claims 7 or 8.
- 25 30

11. The method of claims 9 or 10, wherein the cranberry component comprises whole cranberry powder or whole cranberry extract.

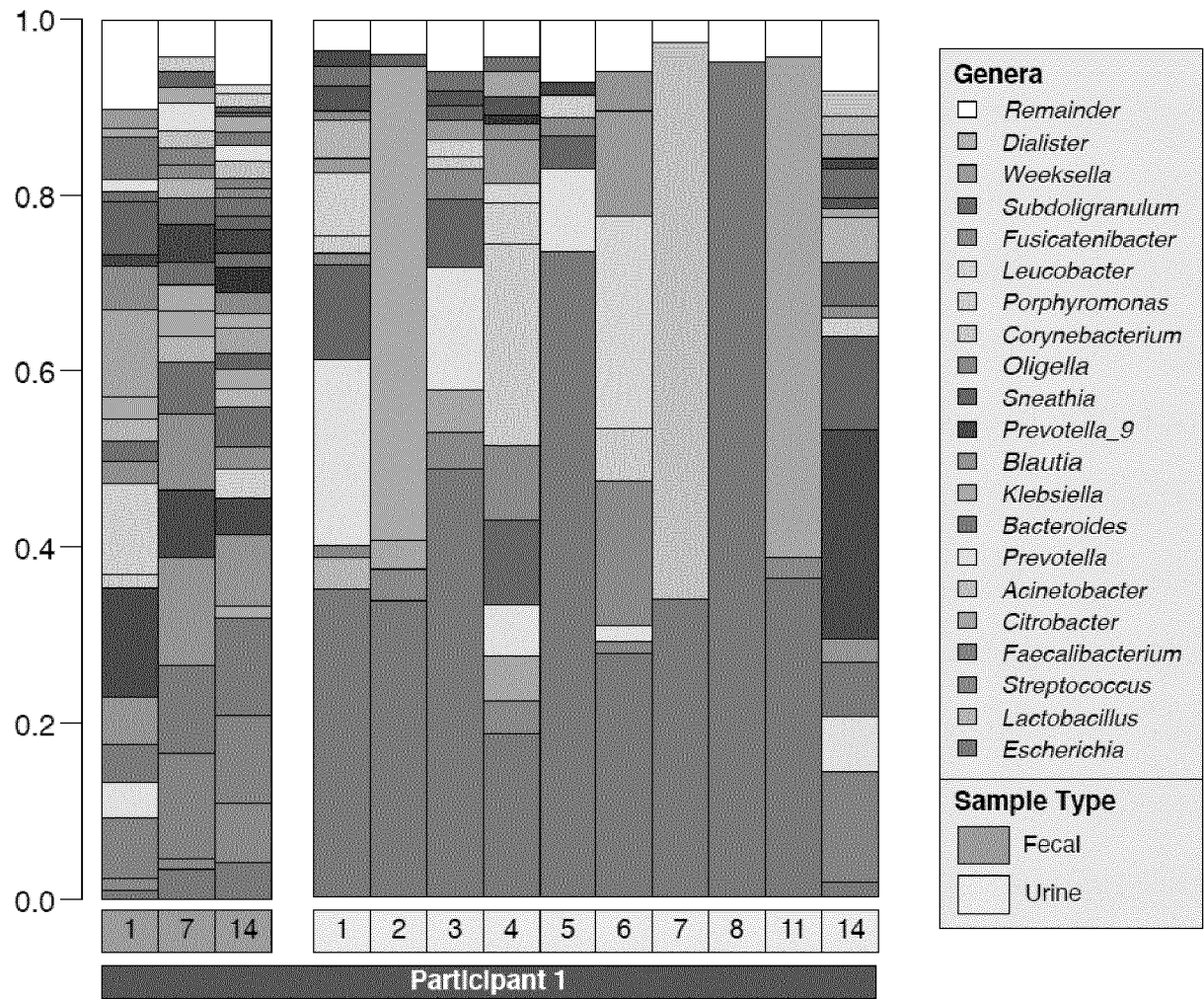
12. The method of any one of claims 9 to 11, wherein the saponin component is quillaja saponin(s).

5 13. The method of any one of claims 9 to 12, that further comprises the administration of a non-steroidal anti-inflammatory agent, an antimicrobial agent and/or an analgesic agent.

14. The method of any one of claims 9 to 12, wherein the composition further comprises a non-steroidal anti-inflammatory agent, an antimicrobial agent and/or an analgesic agent.

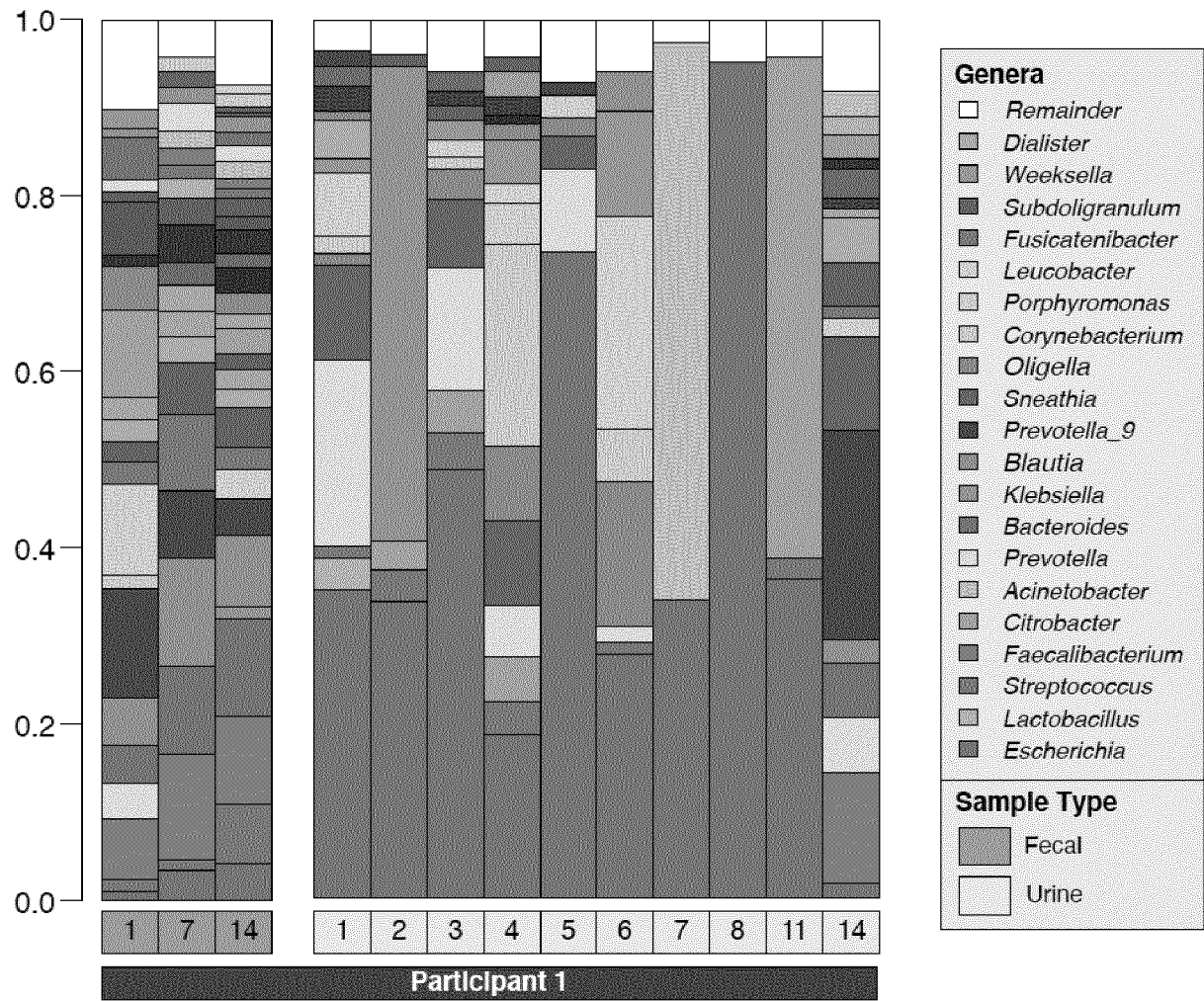
10 15. The method of any one of claims 9 to 12, wherein the composition does not comprise an antimicrobial agent.

16. A method for modulating or adjusting urinary tract and/or gut microbiota and/or reverting urinary tract and/or gut microbiome dysbiosis in a human or animal in need thereof, the method comprising administering to the human or animal an effective amount of a composition according to any of claims 1 to 6 or a pharmaceutical composition or nutraceutical composition
15 according to claims 7 or 8.



5

Figure 1a



5

Figure 1b

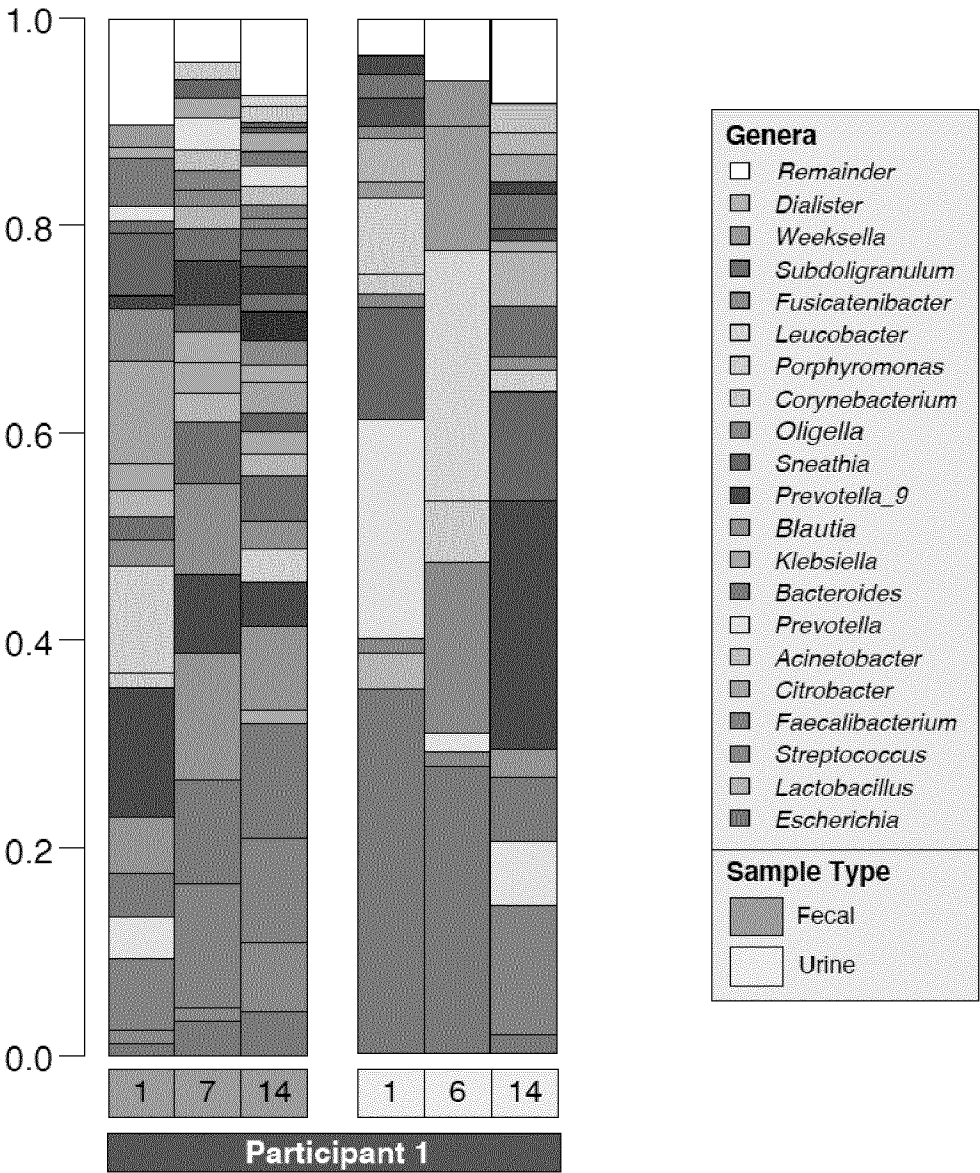


Figure 2a

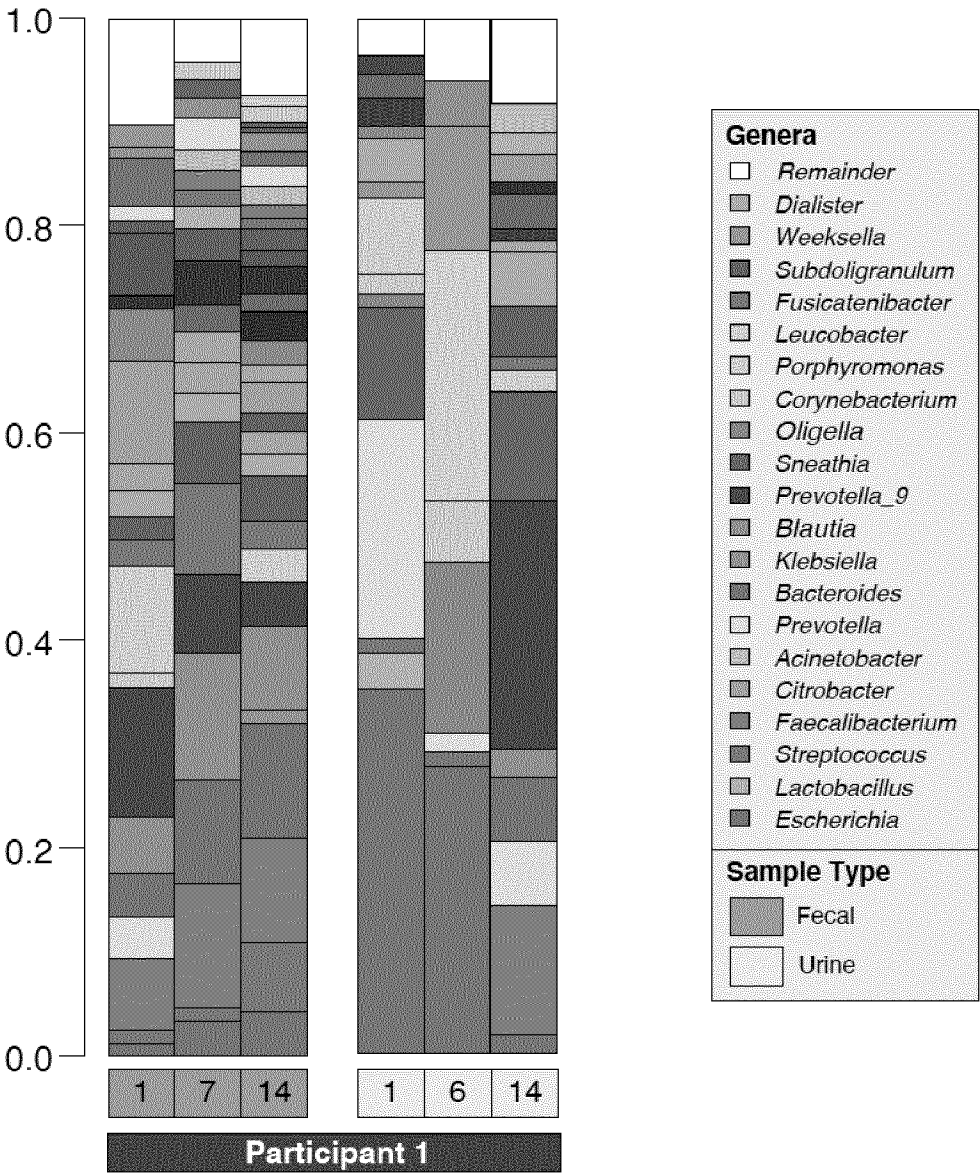


Figure 2b

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/071313

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/45 A61K36/73 A61P13/00 A61P13/08 A61P13/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PASCU (NEAGU) MIHAELA ET AL: "Biologically active extracts with kidney affections applications", APPLIED SURFACE SCIENCE, ELSEVIER, AMSTERDAM, NL, vol. 358, 14 September 2015 (2015-09-14), pages 647-654, XP029325793, ISSN: 0169-4332, DOI: 10.1016/J.APSUSC.2015.09.087 page 648, column 1, paragraph 3 -----	1,9,10, 16
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Further documents are listed in the continuation of Box C.



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"&" document member of the same patent family

Date of the actual completion of the international search

26 November 2021

Date of mailing of the international search report

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Friederich, Martin

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/071313

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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