Impact of cranberry juice consumption on gut and vaginal microbiota in postmenopausal women

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Abstract
Cranberries have long been purported to provide protection against urinary tract infections. There is a line of evidence suggesting that causal pathogens might be seeded from the bacteria reservoirs in the intestinal and vaginal tracts. We tested the hypothesis whether cranberry intake would reshape bacteria taxa in the gut, as well as the vaginal ecosystem. A total of 25 postmenopausal women were enrolled into a randomized, double-blind, placebo-controlled study. Stool samples and vaginal swabs were collected at baseline and after 15 days of consumption of placebo or cranberry beverages, microbiota analyses were performed by Illumina Miseq sequencing following a double-index 16S rRNA gene amplicon. All baseline stool samples generally fell in the Bacteroides enterotype. Significant increases of Prevotella (P = 0.04), Clostridium XIVa members (P = 0.04), Eggerthella (P = 0.03), and Bifidobacterium (P = 0.02) were shown following the cranberry juice intervention; this indicates modulation of the gut microbiota by cranberry components. Baseline vaginal microbiotas fell in three distinct patterns—Lactobacillus dominant, diversified microbiome, and Streptococcus dysbiosis. Compared with the placebo, the cranberry intervention significantly reduced the abundance of pathogenic Streptococcus (P = 0.04) in the dysbiosis group and increased commensal bacteria Anaerococcus, Finegoldia, Actinomyces, and Corynebacterium in the diversified microbiome and dysbiosis groups. Overall, these data suggest that cranberry consumption may improve vaginal microbiota composition in individuals with dysbiosis. Gut-borne taxa stimulation by the combination of cranberry oligosaccharides and polyphenols present in the cranberry product potentially mediates these beneficial properties.

Keywords
cranberries, urinary tract infection, gut microbiota, vaginal microbiota, dysbiosis

1 | INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections among women in general, and postmenopausal women are at increased risk of recurrent infections (Fu et al., 2017; Jung & Brubaker, 2019). It is estimated that more than 50% of women will have at least one occurrence of a UTI during their life spans and approximately 20%–30% are affected with recurrent infections (Beerepoot & Geerlings, 2016; Fu et al., 2017). Although UTIs are generally benign, their prevalence poses medical and economic issues resulting in...
Although pathogenic bacteria, most often Escherichia coli and Streptococcus, are the main UTI causative bacteria, it has been proposed that a reduction in the abundance of commensal vaginal microbes may also contribute to an increased UTI risk in postmenopausal women (Reid, 2018; Stapleton, 2016). It is now well understood that the normal vaginal microbiome is dominated by Lactobacilli, and the vaginal tract is naturally populated with a relatively dense and diverse collection of bacteria (Mendling, 2016; Ravel et al., 2011; White et al., 2011; Witkin & Linhares, 2017). An imbalance of the vaginal microbiome is not only a common cause for bacterial vaginosis (BV) (Stapleton, 2016; White et al., 2011) but may directly affect the potential pathogens to colonize the urethra and/or bladder (Czaja et al., 2009; Stapleton, 2016). Thus, it would appear that asymptomatic changes in the vaginal microbiome may trigger UTI development, either by seeding pathogens or by creating a niche for pathogens to thrive (Czaja et al., 2009; Stapleton, 2016).

The factors shaping the vaginal microbiota composition and stability are still not well known (Braundmeier et al., 2015). In this context, we hypothesize that the vaginal microbiome is strongly influenced by the gut microbiome. There are different lines of evidence to support this hypothesis. First, because of the anatomical proximity, gut microbes in the rectum and distal colon can easily come in contact with the vaginal tract, and indeed several vaginal Lactobacillus species are also found in the digestive tract (Marchesi et al., 2020; Pan et al., 2020). Second, it has become increasingly evident that metabolites produced by the gut microbiome are highly bioavailable and distributed to any organ/region of the human body and these metabolites may influence the vaginal ecosystem as well (Possemiers et al., 2011). Because the gut microbiome is strongly individualized, shaped by external factors, and naturally evolving to some extent, this would in part explain why the underlying causes of UTI and BV are often challenging to identify.

It is plausible that the different responses to cranberry intervention might be the consequence of interindividual differences in gut microbiome composition. During the last decade, reports of potential positive modulation of the human gut microbiota by berries have emerged (Cai et al., 2019; Lavéefre et al., 2020; O’Connor et al., 2019; Rodríguez-Morató et al., 2018). Polymeric cranberry phenolic compounds generally have poor bioavailability. However, when they reach the distal intestine, those molecules are broken down and metabolized by microbiota under anaerobic conditions, a process known as fermentation. Compared to their parent compounds, these bacteria-derived metabolites are highly bioavailable and bioactive. Previous studies showed that γ-valerolactone and its sulfate conjugates (Mena et al., 2017) phenylacetic acid, 3,4-dihydroxyphenylacetic acid (González de Llano et al., 2015), and hippuric and α-hydroxyhippuric acids (González de Llano et al., 2019) have antibacteria effects under experimental conditions. These findings highlight the critical need to understand how cranberries could affect the possible crosstalk between intestinal and other microbiome ecosystems, thereby modulating the impact of dietary cranberries on UTI prevention. This project aimed to assessing the relationships between the gut microbiome and vaginal microbiome, and how cranberry consumption affecting the gut microbiome may also impact the vaginal microbiome. It is expected that in the long term, nutritional studies using other dietary elements (such as prebiotics) may be designed to optimize and maximize the beneficial effects of cranberries.

## Materials and Methods

### Subjects

Twenty-three women volunteered and participated in this study. The eligibility (no menstrual period for at least 12 months) of the participants was determined using a questionnaire. The participants were postmenopausal women between the ages of 50 and 75 years old who met the inclusion criteria including no recent antibiotics or immunosuppressive therapies; surgery of the stomach or small or large intestines; appendectomy, gastric bypass, or gastric banding in the previous 6 months; and diagnosis with any autoimmune diseases.

### Study design and sample collection

This study was a randomized, placebo-controlled, crossover, dietary intervention. Ocean Spray Cranberries, Inc. provided the experimental and placebo beverages, which have been validated and used in previous studies (Hsia et al., 2020; Liu et al., 2019; Maki et al., 2016; Zhao et al., 2020). Both beverages were similar in appearance, taste, and aroma and assigned to volunteers according to computer-generated random orders. Both investigators and participants were blind to the assignment and the products. The products were identified by a random three-digit code preprinted on the cap. The participants consumed either cranberry juice or the placebo beverage daily (8 fl oz per day) for 15 days (Table 1). Analytical methods for testing the products were previously described (Maki et al., 2016). Biological samples were collected

### Table 1: The analytical data for the cranberry and placebo beverages

| Analytical        | Cranberry juice | Placebo | Unit |
|-------------------|-----------------|---------|------|
| Anthocyanins      | 3.09            | ND      | Mg   |
| Flavonols         | 5.68            | ND      | mg   |
| Phenolic acids    | 11.60           | ND      | mg   |
| Total phenolics   | 161             | ND      | mg   |
| Proanthocyanidins | 141             | ND      | mg   |
| Organic acid      | 1.74            | 1.67    | g    |
| Sugar             | 5.94            | 6.3     | g    |

Note: ND indicates nondetectable.
at baseline and after each intervention (Figure 1). Subjects were provided with polyester-tipped swabs with a neutralizing buffer solution using the Environmental Sampling Kit (Puritan Diagnostics, Guilford, ME, USA) for collecting vaginal samples and the Precision™ Stool Collector (Cardinal Health, Dublin, OH, USA) for collecting stool samples. They were also provided with instructions for self-sampling at each sampling event. Vaginal swabs and stool samples were stored at −20°C until used for microbiome analysis.

2.3 DNA extraction

Microbial DNA was extracted from all samples with the QIAamp DNA stool kit (QIAGEN, Valencia, CA, USA) following the manufacturer’s protocol with the addition of cell lysis step to rapidly and completely disrupt cells in the samples to release DNA. The cell lysis was performed by adding 0.1 g of 0.1-mm diameter and 0.1 g of 0.5-mm diameter zirconia–silica beads (BioSpec Products, Bartlesville, OK, USA) to 2-ml tubes. Stool and vaginal samples were transferred to the 2-ml tubes containing zirconia–silica beads. One milliliter of InhibitEX Buffer (from the QIAamp® Fast DNA Stool Mini Kit) was then added to the tubes. The tubes were subjected to a bead-beater for 60 s at maximum speed using a FastPrep®-24 bead-beater (MP Biomedicals, Santa Ana, CA, USA).

The NanoDrop™ 1000 Spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) was used to determine the DNA concentration. Extracted DNA was then visualized following electrophoresis on a 2% agarose gel in 1× TAE (Tris-acetate ethylenediaminetetraacetic acid) buffer (AMRESCO®, Cleveland, OH, USA).

2.4 Universal polymerase chain reaction

16S ribosomal RNA gene was amplified by PCR (95°C for 3 min, followed by 35 cycles at 98°C for 30 s, 55°C for 30 s, and 72°C for 1 min and a final extension at 72°C for 5 min) using primers 8F 5′-AGAGTTTGATCCTGGCTCAG-3′ and 1541R 5′-AAGGAGGTGATCCAGCCGCA-3′ (Carbonero et al., 2014). PCR reactions were performed in 25-µl mixture containing 3 µl of DNA template; 1 µl of each universal primer (8F and 1541R); 12.5 µl of GoTaq® Green Master Mix (Promega™ Corporation, Madison, WI, USA); and 7.5 µl of Nuclease-Free Water. Amplicons were run on agarose gel electrophoresis to confirm the success of the PCR by using 1 µl of SYBR safe DNA Gel Stain (Thermo Fisher Scientific) fluorescent dye.

2.5 Libraries preparation and sequencing

For 16S rRNA gene sequencing analyses, a dual-indexed amplicon strategy was performed using universal primers tagged with Illumina adapters and barcodes as described before (Aljahdali et al., 2017; Kozich et al., 2013; Mayta-Apaza et al., 2018). Briefly, PCR was set up in 25 µL reaction components with 3 µl of the DNA template; 2.5 µl of the AccuPrime™ PCR buffer II; 0.5 µl of each index primers; 0.1 µl of AccuPrime™ Taq DNA Polymerase (Invitrogen, Waltham, MA, USA); and 18.4 µl of Nuclease-Free Water following the recommended protocol. The PCR consisted of initial denaturation at 95°C for 3 min, followed by 30 cycles of denaturation at 95°C for 30 s, primer annealing at 55°C for 30 s, and an extension at 72°C for 1 min, with a final extension step at 72°C for 5 min. Correct size amplicons were subjected to purification and normalization with the Invitrogen SequaPrep kits following the manufacturer’s protocol. Amplicons were pooled into two different libraries and concentrations were measured by Agilent bioanalyzer and qPCR using the same primers and PerfeCta NGS library quantification kits (Quanta Biosciences, Beverly, MA, USA). Libraries were then denatured and diluted to appropriate concentrations and sequenced on an Illumina MiSeq.

Resulting sequencing files were analyzed using the Mothur software. Operational taxonomic units were determined and classified against reference databases (Ribosomal Database Project [RDP],
TABLE 2  Volunteers demographics

| Age (years) | BMI          | Height (inches) | Weight (lbs) |
|------------|--------------|-----------------|--------------|
| 61 ± 7     | 28.5 ± 7.8   | 64.2 ± 2.3      | 170.5 ± 49.7 |

The human study was completed with 23 volunteers, and 21 of which provided the full set of samples. The volunteers’ demographics are described in Table 2.

3 | RESULTS AND DISCUSSION

The vaginal microbiotas were found to be extremely heterogeneous at baseline, and have therefore been stratified into three groups based on the most abundant genera and their known relation to vaginal health (Figure 3).

3.2 | Impact of the cranberry juice on the vaginal microbiota

The vaginal microbiotas of these subjects was significantly more diverse at baseline, and have therefore been stratified into three groups based on the most abundant genera and their known relation to vaginal health (Figure 3).

Group 1 comprises individuals whose baseline vaginal microbiotas were strongly dominated by Lactobacillus, which is considered the ideal healthy state (Ravel et al., 2011). Group 2 comprises individuals whose baseline vaginal microbiotas were characterized by diverse and relatively well-distributed high number of different taxa, without obvious dominant detrimental genus. Group 3 comprises individuals whose baseline vaginal microbiotas were characterized by high abundance of Streptococcus, which is strongly indicative of microbial dysbiosis that could potentially lead to vaginosis or UTI (Leclercq et al., 2016; Tan et al., 2012; Ulett et al., 2009). Individuals were roughly equally distributed among the three groups, which allowed statistical analyses for each group.

3.2.1 | Lactobacillus-dominant vaginal microbiota

Consumption of both products appeared to have little impact on the vaginal microbiota of volunteers that have Lactobacillus as the major bacterial taxa (Figure 4).

3.2.2 | Diverse baseline vaginal microbiota

As expected with the criterion used to segregate the groups, the vaginal microbiota of these subjects was significantly more diverse (Figure 5). The number of taxa was significantly decreased after the consumption of cranberry juice (El Aidy et al., 2013; Rivière et al., 2016; Walker et al., 2014) (Figure 2). Butyrate is a short-chain fatty acid shown to offer benefits to not only the local intestinal environment but also contributes to systemic metabolism (Liu et al., 2018; O’Keefe, 2016). Akkermansia, a genus that has been associated with a number of health properties, was increased with cranberry consumption in animal models (Anhé et al., 2017; Rodríguez-Daza et al., 2020) and to some extent in humans (Bekiares et al., 2018). It showed a slight but nonsignificant increase between cranberry and placebo beverages (Dao et al., 2016; Png et al., 2010) (Figure 2). It should be noted that all those trends were strongly individualized, and further validation is warranted in more clinical studies with a larger sample size. Overall, cranberry consumption appears to stimulate beneficial genera.
FIGURE 2  Impact of cranberry juice and placebo on the relative abundance of genera from Actinobacteria, Bacteroidetes, Verrucomicrobia, and Firmicutes. Values are expressed as mean ± standard error (SE) (n = 8). Different letters indicate significant difference (P < 0.05), whereas N.S. indicates no significant difference. BL, baseline; CR, cranberry; PL, placebo
**FIGURE 3** Nonmetric multidimensional scaling (Bray–Curtis index) showing the three different clusters of baseline vaginal microbiota.

**FIGURE 4** Diversity indices and changes in relative abundances in volunteers with *Lactobacillus*-dominated vaginal microbiota. Values are expressed as mean ± standard error (SE) (n = 8). Different letters indicate significant difference (P < 0.05), whereas N.S. indicates no significant difference. BL, baseline; CR, cranberry; PL, placebo.
extent; but the loss of the diversity does not appear to be different between the interventions and thus, it is likely not associated with cranberry components.

Several significant changes were observed in the bacteria abundance at genus level (Figure 6). Compared with baseline, consumption of cranberry juice allowed for the maintenance of several moderately abundant Firmicutes (Lactobacillus, Anaerococcus, Finegoldia, and Peptoniphilus) and Actinobacteria (Actinomyces, Varibaculum, Actinomycetales, and Corynebacterium). In contrast, aforementioned bacteria were significantly reduced following placebo beverage consumption. Different responses between the cranberry and placebo beverage from baseline were statistically significant. The status of these genera is somewhat controversial, but they would be considered as mostly harmless to vaginal health (Boskey, 2001; Ma et al., 2012). The placebo
beverage led to an unexplainable increase of *Prevotella*, which was different from the response following cranberry beverage intake. *Prevotella* in the gut microbiota are associated with plant-based diets with a possible role in digestion of complex carbohydrates and production of short-chain fatty acids (Geva-Zatorsky et al., 2017; Precup & Vodnar, 2019; Zhu et al., 2015). However, the function of *Prevotella* in the vaginal tract is less clear. Some lines of evidence suggested that high levels of short-chain fatty acids might promote dysbiosis and inflammation in the vaginal tract (Aldunate et al., 2015; Amabebe & Anumba, 2020). To conclude, cranberry juice appears to maintain the diversity of vaginal microbiota, which is a possibly healthier profile for these volunteers.

**FIGURE 7** Diversity indices changes in subjects with *Streptococcus* dysbiosis. Values are expressed as mean ± standard error (SE) (*n* = 7). Different letters indicate significant difference (*P* < 0.05), whereas N.S. indicates no significant difference. BL, baseline; CR, cranberry; PL, placebo.

**FIGURE 8** Impact of cranberry juice and the placebo on the relative abundance of the major genera in subjects with *Streptococcus* dysbiosis at baseline. Values are expressed as mean ± standard error (SE) (*n* = 7). Different letters indicate significant difference (*P* < 0.05), whereas N.S. indicates no significant difference. BL, baseline; CR, cranberry; PL, placebo.
3.2.3  |  Streptococcus dysbiosis

Several women (n = 7) were found to have a strong dysbiosis of their vaginal microbiota, characterized by a high initial abundance 22%–81% of Streptococcus, a well-known causative agent of vaginosis and UTI (Jass & Reid, 2009; Leclercq et al., 2016; Tan et al., 2012; Ulett et al., 2009).

As suggested by the diversity trends, cranberry juice had a very strong and specific impact on the dysbiosed vaginal microbiota (Figure 7). Most notably, although both beverages reduced the abundance of Streptococcus compared to baseline, the consumption of cranberry juice significantly reduced the relative abundance of Streptococcus to a greater extent, compared to the placebo beverage. Intriguingly, it appeared that Streptococcus has been replaced with a range of different Firmicutes (Anaerococcus and Finegoldia) and Actinobacteria (Actinobaculum, Actinomyces, Varibaculum, and Corynebacterium; Figure 8). Streptococcus, both group A and B, colonization has been associated with an increased risk of vaginitis, BV, through the female life span (Clark & Atendido, 2005; Verstraeten et al., 2011). The presence of this genus also significantly increased chances of vertical transmission to neonates during pregnancy (Puupolo et al., 2019). The exact mechanism of the reduction of the abundance of Streptococcus by cranberries is unknown. However, Feliciano and colleagues showed that cranberry proanthocyanidins (PAC) reduced extra-intestinal pathogenic E. coli agglutination and inhibited the invasion of enterocytes (Feliciano et al., 2014). Cranberry-derived PACs might impair virulence and quorum sensing of Pseudomonas aeruginosa, according to another study (Maisuria et al., 2016). In the research performed by O’May and Tufenkji, cranberry PAC and other tannin-containing materials blocked swarming motility of P. aeruginosa, possibly via inhibition of the flagellin gene expression (O’May & Tufenkji, 2011). It can be hypothesized that cranberries and metabolites generated and absorbed in the gut affected Streptococcus through multiple mechanisms, inhibition of bacteria growth or viability, disruption of cytoskeleton structure, and so forth. These hypotheses will warrant future experiments to explore.

4  |  CONCLUSION

These findings suggest a beneficial impact of cranberry juice on vaginal microbiota with dysbiosis, and possibly its contribution to vaginal health. It can be speculated that Streptococcus dysbiosis could be improved directly within the local niche environment by increasing competition of other commensal bacteria or indirectly by decreasing the bacteria migration from the gut reservoir, and thereby restoring a healthier vaginal microbiota. Due to that possible relationship, the beneficial impact of cranberry juice on the gut microbiota is also encouraging for vaginal health. As reported previously, the ageing gut microbiota tends to be less diverse and responsive to dietary changes. Herein, a relatively short-term consumption and daily consumption of cranberry juice shows promising prebiotic effect and may help maintain levels of a wide range of beneficial genera (Prevotella, Bifidobacterium, and butyrate-producing Firmicutes).

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AUTHOR CONTRIBUTIONS

Franck Carbonero conceptualized and visualized the study and acquired funding. Ayoub Al Othaim and Franck Carbonero wrote the original draft. Ayoub Al Othaim, Daya Marasini, and Franck Carbonero collected the data, contributed in formal analysis and methodology, and reviewed and edited the manuscript. Daya Marasini and Franck Carbonero administered the project and supervised the study.

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