

## RESEARCH PROTOCOL

<b>Date</b>	2/20/21
<b>Title</b>	Methenamine Hippurate with Cranberry Capsules versus Cranberry Capsules alone for UTI prevention in a short-term indwelling Foley catheter population after Urogynecological surgery: A Double-Blinded Randomized Controlled Trial
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<b>Hatton #</b>	18-115

IRB Review Type:  Exempt  Expedited  Full Board

### Purpose of Study

- **Primary Aim:** To assess if oral Methenamine Hippurate (MH) in combination with cranberry capsules is superior to cranberry capsules alone in prevention of UTI in patients with transient post-operative urinary retention requiring a Foley catheter after pelvic reconstructive surgery.
  - **Secondary Aims:**
    - To assess patient adherence to the interventions.
    - To assess patient satisfaction associated with the different interventions.

### Hypothesis or Research Question

- We hypothesize that daily oral MH and cranberry therapy will be a superior treatment to cranberry alone in the prevention of UTI in patients with short term indwelling Foley catheters after pelvic reconstructive surgery.

### Background

Urinary tract infections (UTIs) are one of the most common bacterial infections in women [1]. It is estimated that 1.6 billion dollars are spent on UTI treatment each year [2-3]. *Escherichia coli* (*E.coli*), a gram negative bacterium, is the most common pathogen found amongst those diagnosed with UTIs. Research suggests that 70-95% of UTIs are attributed to *E.coli* which originates from intestinal microflora [4-7]. Additionally, the more virulent strains of *E.coli* express type 1 and p-fimbriae, which aid in adhesion to the urothelium [8-12]. Antibiotics have been the mainstay of treatment of UTIs, however frequent use has increased the prevalence of antibiotic resistant organisms [3-4]. Therefore, focus has shifted to non-antibiotic therapy for UTI prophylaxis.

Methenamine Hippurate (MH) has been studied for decades due to its potential role in prevention of UTI. While not technically an antibiotic, MH works via its bacteriostatic action in the bladder. MH's breakdown products include ammonium and formaldehyde [13-15] which

are most effective at a urine pH below 5.5 [16-18]. Benefits of MH are the lack of development of resistance, and the selective nature of this drug to the urinary system only. However, MH is best used in conjunction with an acidifying agent to increase its bioavailability (such as cranberry capsules or other acidic products) [14-18].

The usage of MH has been studied in various populations, has been seen to be effective in short-term catheterization [15]. One study by Schiotz, et. al revealed that in patients after gynecological surgery that required 24 hours of Foley catheter placement had an incidence of UTI in 13.9% of patients with placebo versus 2.7% of patients using MH [19]. Although there is some evidence of benefit, a Cochrane Database review revealed there was significant heterogeneity between studies and many of these studies vary in aspects such as definition of UTI and dosage of MH. Many prior studies did not combine MH with an acidifying agent, which could also limit its efficacy [14].

The American cranberry (*Vaccinium macrocarpon*) is another non-antibacterial agent which has been widely studied [8]. Cranberries are composed of ingredients that include fructose, anthocyanidins and proanthocyanidins [8, 20]. These components are proposed to affect adhesion proteins that are expressed by bacteria, such as *E.coli*, and prevent the development of infection [8, 20, 28-30].

Usage of cranberry as prophylaxis for UTI is controversial; however, results have been favorable in the post-operative gynecological population. One such study by Foxman et al. revealed that the incidence of UTI was significantly lower in the cranberry than placebo group (19% versus 38%) after undergoing gynecological surgery [32]. Additionally, the 7 patients who required an indwelling catheter at time of discharge were found to have lower rates of UTI than placebo (1 of 3 versus 3 of 4, respectively) [32]. However, a study from our center revealed that real-time prescriptions of cranberry to postoperative patients with catheters did not significantly reduce UTI rates [33].

Post-operative urinary retention (POUR) occurs frequently in patients who undergo incontinence and pelvic prolapse surgery [34-36]. Although the definition of POUR can vary between clinicians, it is reported as 2.5-24% to as high as 43% after tension-free transvaginal mesh sling placement [34, 36, 37]. This population is also at high risk for UTI due to advanced age and menopausal status [34, 38, 39]. Finally, using a catheter longer than 2 days incurs a 2-fold increased risk of development of UTI with an estimated 5% increase in bacteriuria each day of catheterization [32, 34, 40-41].

Moreover, although the incidence of UTI after pelvic reconstructive surgery ranges from 10% to 64% [42], a retrospective review performed at our institution revealed our incidence of UTI was as high as 72% [33]. In hopes to decrease the overuse of antibiotics and decrease the likelihood of antibiotic resistance, we propose that the use of MH and cranberry can reflect a potential benefit in this population of short-term indwelling Foley catheter use and help reduce the incidence of post-operative UTI after pelvic surgery.

## Research Plan

- **Study Design**

- Randomized double-blinded placebo-controlled trial

- **Setting for the study**

- All patients will be approached for enrollment into the study if they fail their retrograde void trial (VT) after major pelvic reconstructive surgery for pelvic organ prolapse during their hospital stay
- The patients will then be randomized to either receive cranberry capsules and placebo OR cranberry capsules and Methenamine Hippurate.
- The research nurse will be blinded to the group allocation.
- Patients will be instructed to take the pills assigned to them twice daily until their repeat retrograde VT in the office (6-8 days).
- A catheterized urine specimen will be then collected on the day of the retrograde void trial on or about postoperative day 7.
- Patients will be asked to return the pill bottles at their catheter removal visit, on or about postoperative day 7.
- At the end of the retrograde VT, patients will be given a questionnaire to complete regarding their experience with the medication randomized to them and satisfaction with the medication.
- At 2 weeks postoperatively, the patients will have a clean-catch urine specimen during their routine postoperative visit and this will be recorded.
- Patients' charts will be followed until their 6-week post-operative visit.
- Symptomatic or culture proven urinary tract infections detected during the research period will be treated with the appropriate antibiotics as standard of care, based on the judgment of the treating provider.

- **Participants**

Study population is women between 18 years old and 90 years old.

Inclusion Criteria:

- Patients who undergo major pelvic organ prolapse surgery that are diagnosed with POUR via failed retrograde void trial and require an indwelling Foley catheter upon hospital discharge.

Exclusion Criteria:

- Unwillingness to participate in the study.
- Inability to understand English.
- Pregnant women
- Patient personal history of nephrolithiasis, urogenital anomaly, neurogenic bladder, chronic renal insufficiency (GFR <60 ml/min/1.73 m<sup>2</sup>), sarcoidosis, and severe hepatic insufficiency.
- Currently (prior 3 months) undergoing medical management for recurrent UTI or interstitial cystitis
- Current antibiotic use over the last month for additional medical issues.

- Active urinary tract infection.
- Patient history of taking Warfarin (Coumadin).
- Intraoperative bladder injury or cystotomy
- Physical or mental impairment that would affect the subject's ability to take medications daily or fill out questionnaires.
- Reported allergy to any of the ingredients in the cranberry, MH, or placebo pill
- Sample Size
  - A sample size was calculated to be 88 patients in each arm based on the following:
    - A prior study by Foxman et al. evaluated incidence of UTI of patients who underwent various benign gynecological surgeries who had placement of an indwelling urinary catheter. These patients were randomized to either receive TheraCran cranberry capsules or placebo for 6-8 weeks duration [32].
    - Two group  $\chi^2$  test with a 0.050 two-sided significance level was used for sample size calculation.
    - The power was set to 80%
    - Assuming an estimated drop-out rate of 15%, the number of patient enrollment per arm was set to 104, for a total of 208 patients total
- **Data Collection**
  - **Primary Outcome:**
    - Incidence of UTIs requiring treatment in each group, diagnosed during the first (approximately) one week of short-term indwelling Foley catheter in the post-operative period after undergoing major pelvic reconstructive surgery.
  - **Secondary Outcome:**
    - Adherence to the medication regimen provided
    - Patient satisfaction with medication regimen provided
    - Adverse effects that patients encountered during study period
    - Number of patients who are diagnosed and treated for UTI in the 6-week post-operative period following surgery
  - **General Demographic Data:**
    - Age, weight, height, BMI, ethnicity, past medical history, social history, preoperative stage of prolapse (POPQ), type of surgical procedure, duration of Foley catheter therapy, post-operative complications, UTI

symptoms, urine acidity (pH), diagnosis of overactive bladder, post void residual (PVR) before surgery, POD1 and on or about POD7.

- **Intervention or experimental aspect of the study**

- All patients of Cincinnati Urogynecology Associates who undergo pelvic organ prolapse repair(s) and have a retrograde VT prior to discharge per standard practice. The retrograde VT will be performed by the nursing staff. Per protocol, up to 300ml sterile saline will be instilled into the bladder and the indwelling urinary catheter will be removed. Patients will be allotted 30 minutes to void. The instilled volume, voided volume, and PVR if needed will be recorded.
- Failure of the retrograde VT is defined by inability to void two-thirds of the instilled volume or PVR greater than 100mL.
- Patients who fail the retrograde VT will then be approached for the study by one of the investigators or trained Research Nurse.
- An indwelling urinary catheter will be reinserted and the patient will be taught on its use and care by the nursing staff.
- If the patient agrees to participate in the study, the patient will be randomized to either receive either the MH and Cranberry or Cranberry and placebo.
- Based on a randomization list, the patient will be assigned a Study ID and the medications will be distributed by the inpatient pharmacy to the patient prior to their discharge.
- The medications will have a label which will be generated by the pharmacy that includes the name of the patient, name of the medication group allocation, (Ex. Med A) expiration date and study ID.
- These medications will be added onto their discharge instructions via a Medication Reconciliation on EPIC.
- All subjects will be provided all other routine prescriptions for pain medication, bowel regimen and instructions on how to administer the medication given.
- Patients will be advised to take the medication roughly at the same time each day with food to aid in absorption.
- On or about POD7, the patient will be asked to return to the office for a repeat retrograde VT (as described above).
- A catheterized urine specimen will be collected on this visit and recorded.
- If the patient fails the retrograde VT on or about POD7 they will have the catheter replaced. Additionally, they will be recommended to continue Cranberry supplementation as per our current routine practices until they return on their two-week postoperative visit to repeat the retrograde VT (as described above). They will however not be asked to continue MH or the placebo pills during this time.

- Patients will fill out a questionnaire based on the Medicine Acceptability Questionnaire as well as UTI symptoms experienced and overall satisfaction [43].
- Two-week postoperative visit
  - All patients will have a routine examination at 2 weeks with a clean catch urine specimen
  - All patients will have urine dip performed on the PVR urine sample. If positive for leukocyte esterase, white blood cells, or nitrites, the urine dip will be sent to the laboratory for culture. All urine culture results will be reviewed and if positive, will be treated and recorded.
- Six-week postoperative visit
  - All patients will be asked to present for routine 6-week post-operative visit.
- As per standard practice at our office, patients will be advised to report symptoms such as dysuria, fever, flank pain, hematuria, frequency or urgency, cloudy urine, hematuria, or abdominal pain,. During business hours they will be asked to call the office staff, while other times they will page the on-call physician.
- During operating hours, the office staff will arrange a clinic visit for the same day at one of four outpatient clinics (Clifton, West Chester, Kenwood, Anderson) and obtain a urine sample prior to the start of antibiotic therapy.
- If not during office hours, the on-call staff will either direct the patient to a facility for urine collection prior to the start of antibiotic therapy, or if unable to do so, start antibiotic therapy based on clinical symptoms.
- During any antibiotic therapy the patients will be advised to STOP all study medications
- All of these encounters will be recorded.
- **Experimental oral capsules**
  - Methenamine Hippurate 1g (1 tablet BID)
    - Contains Hippuric acid salt of Methenamine (hexamethylene tetramine), Magnesium Stearate, Povidone, Saccharin Sodium, FD&C Yellow No. 5 (Tartazine) [44].
    - >90% of methenamine is excreted in the urine within 24 hours after administration [44].
    - Side effects are generally mild and are found in 3.3% of patients. These include gastrointestinal upset, dysuria, abdominal cramps, and rash which are reversible [44].
    - Sulfonamides are to be used with caution with Methenamine as it has been shown that it concurrent use may cause a decrease in efficacy of the Methenamine by alkalization of the urine [44].
  - Placebo Pill

- Nature Made Super Strength Cranberry 450mg Extract (1 Tablet BID)
      - Side effects are generally mild and include stomach/abdominal upset, diarrhea. Kidney stones may occur but is associated with higher high doses [46].
      - There have been case reports regarding hypercoagulability with high doses of Cranberry concomitant Warfarin therapy [47].
  - Urinary Tract Infection (UTI) [48]
    - Definition will include bacteriuria will be presence of bacteria at clinically relevant levels, or treatment with antibiotic for suspected UTI by a provider
      - Possible associated symptoms patients may complain of include: dysuria, suprapubic pressure/pain, fever >100.4, urinary frequency or urgency.
- **Statistical Analysis**
  - Descriptive statistics will be generated for demographic information such as age, race, BMI etc. Chi-squared test or Fisher's exact test will be employed to examine the difference in categorical variables between two groups. A Shapiro-Wilk test will be performed for testing normality. To test the difference in continuous variables between two groups, Student t-test or a Mann-Whitney test will be used. A Logistic regression will be implemented to calculate the odds ratio and corresponding confidence interval for comparing the incidence of UTI between two groups.

## Ethical Considerations

- **Informed consent**
  - Patients who agree to participate in the study will sign a written informed consent. They will be consented by one of the stated investigators or trained Research Nurse and they will receive a copy of the signed informed consent statements (ICS). A copy will be put in their medical file.
- **Privacy information**
  - Extensive efforts will be made to ensure and maintain participant confidentiality. All identifying information will be maintained in a secure area at all times. Source documentation will be maintained in a separate folder. When documentation has to be made available for data analysis, copies of the source (Excel spreadsheets) with only Subject ID number visible and personal information obscured will be used. All communication between staff members regarding participant data will occur via the Subject ID number only. However, identifying information will be retained in the original/source documents.

- The participant will be logged in the Excel spreadsheet and assigned a Subject ID number. Each participant will be assigned the next available Subject ID number. Once each Subject ID number has been assigned, it will not be reassigned. The Excel spreadsheet will be stored on a password protected, encrypted TriHealth computer for ten years following study closure, and then purged.

<b>Estimated Period of Time to Complete Study</b>	
<b>When will study begin?</b>	June 2019
<b>Protocol Development Completed</b>	December 18, 2018
<b>Admin Review Time</b>	2 weeks
<b>IRB Approval</b>	January 8 <sup>th</sup> , 2018
<b>Data collection</b>	Subjects to be enrolled starting June 2019
<b>Data analysis</b>	January 2021

- **When and how will results be disseminated?**
  - Submit for abstract presentation at national/international meeting and publication

## References

- [1] Leckie, K. What is the evidence for the role of oestrogen in the prevention of recurrent urinary tract infections in postmenopausal women? An evidence-based review. *Journal of Clinical Gerontology and Geriatrics*. 2010 Dec; 1(2):31-35.
- [2] Foxman B. Epidemiology of urinary tract infections: Incidence, morbidity and economic costs. *Am J of Med*. 2002;113:5S-13S [PubMed:12113866]
- [3] Borchert, D, et al. "Prevention and Treatment of Urinary Tract Infection with Probiotics: Review and Research Perspective." *Indian Journal of Urology*, vol. 24, no. 2, 2008, p. 139., doi:10.4103/0970-1591.40604.
- [4] Ng, Qin Xiang, et al. "Use of Lactobacillus Spp. to Prevent Recurrent Urinary Tract Infections in Females." *Medical Hypotheses*, vol. 114, 2018, pp. 49–54., doi:10.1016/j.mehy.2018.03.001.
- [5] Bartoletti, Riccardo, et al. "Treatment of Urinary Tract Infections and Antibiotic Stewardship." *European Urology Supplements*, vol. 15, no. 4, 2016, pp. 81–87., doi:10.1016/j.eursup.2016.04.003.
- [6] Vahlensieck, Winfried, et al. "Management of Uncomplicated Recurrent Urinary Tract Infections." *European Urology Supplements*, vol. 15, no. 4, 2016, pp. 95–101., doi:10.1016/j.eursup.2016.04.007.
- [7] Köves, Béla, and Björn Wullt. "The Roles of the Host and the Pathogens in Urinary Tract Infections." *European Urology Supplements*, vol. 15, no. 4, 2016, pp. 88–94., doi:10.1016/j.eursup.2016.04.005.



- [8] Hisano, M, et al. "Cranberries and Lower Urinary Tract Infection Prevention." *Clinics*, vol. 67, no. 6, Dec. 2012, pp. 661–667., doi:10.6061/clinics/2012(06)18.
- [9]. Schmidt DR, Sobota AE. An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates. *Microbios*. 1988;55(224-225):173–81. [[PubMed](#)]
- [10] Zafirri D, Ofek I, Adar R, Pocino M, Sharon N. Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated *Escherichia coli* to eucaryotic cells. *Antimicrob Agents Chemother*. 1989;33(1):92–8. [[PMC free article](#)] [[PubMed](#)]
- [11] Pinzon-Arango PA, Liu Y, Camesano TA. Role of cranberry on bacterial adhesion forces and implications for *Escherichia coli*-uroepithelial cell attachment. *J Med Food*. 2009;12(2):259–70. [[PubMed](#)]
- [12] Ofek I, Mirelman D, Sharon N. Adherence of *Escherichia coli* to human mucosal cells mediated by mannose receptors. *Nature*. 1977;265(5595):623–5. [[PubMed](#)]
- [13] Saint, Sanjay, and Benjamin A. Lipsky. "Preventing Catheter-Related Bacteriuria." *Archives of Internal Medicine*, vol. 159, no. 8, 1999, p. 800., doi:10.1001/archinte.159.8.800.
- [14] Lee, B, et al. "Methenamine Hippurate for Preventing Urinary Tract Infections." *The Cochrane Database of Systematic Reviews (Protocol)*, 2002, doi:10.1002/14651858.cd003265.
- [15] Bennett, John E., et al. *Mandell, Douglas, and Bennetts Principles and Practice of Infectious Diseases*. Elsevier / Saunders, 2015.
- [16] Greenwood, D., and R. C. B. Slack. "The Antibacterial Activity of Hexamine (Methenamine), Hexamine Hippurate and Hexamine Mandelate." *Infection*, vol. 9, no. 5, 1981, pp. 223–227., doi:10.1007/bf01640720.
- [17] Hetey SK. Effect of ascorbic acid on urine pH in patients with injured spinal cords. *American Journal of Hospital Pharmacy* 1990;37(2):235-7.
- [18] Wall I, Tiselius HG. Long-term acidification of urine in patients treated for infected renal stones. *Urologia Internationalis* 1990;45(6):336-41.
- [19] Schiotz, Hjalmar A., and Kristian Guttu. "Value of Urinary Prophylaxis with Methenamine in Gynecologic Surgery." *Acta Obstetrica Et Gynecologica Scandinavica*, vol. 81, no. 8, 2002, pp. 743–746., doi:10.1034/j.1600-0412.2002.810810.x.
- [20] Guay DR. Cranberry and urinary tract infections. *Drugs*. 2009;69(7):775–807. [[PubMed](#)]
- [21] Bruyere F. [Use of cranberry in chronic urinary tract infections] *Med Mal Infect*. 2006;36(7):358–63.[[PubMed](#)]
- [22] Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ*. 2001;322(7302):1571. [[PMC free article](#)] [[PubMed](#)]
- [23] Jepson RG, Craig JC. A systematic review of the evidence for cranberries and blueberries in UTI prevention. *Mol Nutr Food Res*. 2007;51(6):738–45. [[PubMed](#)]
- [24] Cimolai N, Cimolai T. The cranberry and the urinary tract. *Eur J Clin Microbiol Infect Dis*. 2007;26(11):767–76. [[PubMed](#)]
- [25] Gupta K, Chou MY, Howell A, Wobbe C, Grady R, Stapleton AE. Cranberry products inhibit adherence of p-fimbriated *Escherichia coli* to primary cultured bladder and vaginal epithelial cells. *J Urol*. 2007;177(6):2357–[26][[PMC free article](#)] [[PubMed](#)]
- [27] Di Martino P, Agniel R, David K, Templer C, Gaillard JL, Denys P, et al. Reduction of *Escherichia coli* adherence to uroepithelial bladder cells after consumption of cranberry juice: a

- double-blind randomized placebo-controlled cross-over trial. *World J Urol.* 2006;24(1):21–7. [\[PubMed\]](#)
- [28] Foo LY, Lu Y, Howell AB, Vorsa N. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated *Escherichia coli* in vitro. *Phytochemistry.* 2000;54(2):173–81. [\[PubMed\]](#)
- [29] Howell AB, Vorsa N, Der Marderosian A, Foo LY. Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. *N Engl J Med.* 1998;339(15):1085–6. [\[PubMed\]](#)
- [30] Foo LY, Lu Y, Howell AB, Vorsa N. A-Type proanthocyanidin trimers from cranberry that inhibit adherence of uropathogenic P-fimbriated *Escherichia coli*. *J Nat Prod.* 2000;63(9):1225–8. [\[PubMed\]](#)
- [31] Wang, Chih-Hung, et al. “Cranberry-Containing Products for Prevention of Urinary Tract Infections in Susceptible Populations.” *Archives of Internal Medicine*, vol. 172, no. 13, Sept. 2012, doi:10.1001/archinternmed.2012.3004.
- [32] Foxman, Betsy, et al. “Cranberry Juice Capsules and Urinary Tract Infection after Surgery: Results of a Randomized Trial.” *American Journal of Obstetrics and Gynecology*, vol. 213, no. 2, 2015, doi:10.1016/j.ajog.2015.04.003.
- [33] Shatkin-Margolis, Abigail, et al. “Cranberry Supplementation Does Not Reduce Urinary Tract Infections in Patients With Indwelling Catheters After Pelvic Reconstructive Surgery.” *Female Pelvic Medicine & Reconstructive Surgery*, vol. 24, no. 2, 2018, pp. 130–134., doi:10.1097/spv.0000000000000507.
- [34] Geller, Elizabeth J. “Prevention and Management of Postoperative Urinary Retention after Urogynecologic Surgery.” *International Journal of Womens Health*, 2014, p. 829., doi:10.2147/ijwh.s55383.
- [35] Buchko, Barbara L., and Leslie E. Robinson. “An Evidence-Based Approach to Decrease Early Post-Operative Urinary Retention Following Urogynecology Surgery.” *Urologic Nursing*, vol. 32, no. 5, 2012, p. 260., doi:10.7257/1053-816x.2012.32.5.260.
- [36] Dorflinger A, Monga A. Voiding dysfunction. *Curr Opin Obstet Gynecol.* 2001;13(5):507-512.
- [37] Partoll, Linda M. “Efficacy of Tension-Free Vaginal Tape with Other Pelvic Reconstructive Surgery.” *American Journal of Obstetrics and Gynecology*, vol. 186, no. 6, 2002, pp. 1292–1298., doi:10.1067/mob.2002.123736.
- [38] Wu, Jennifer M., et al. “Lifetime Risk of Stress Urinary Incontinence or Pelvic Organ Prolapse Surgery.” *Obstetrics & Gynecology*, vol. 123, no. 6, 2014, pp. 1201–1206., doi:10.1097/aog.0000000000000286.
- [39] Ketia H, et al. “Predictive Factors of Early Postoperative Urinary Retention in the Postanesthesia Care Unit.” *Survey of Anesthesiology*, vol. 49, no. 6, 2005, pp. 329–330., doi:10.1097/01.sa.0000185372.31470.db.
- [40] Wald, Heidi L. “Indwelling Urinary Catheter Use in the Postoperative Period.” *Archives of Surgery*, vol. 143, no. 6, 2008, p. 551., doi:10.1001/archsurg.143.6.551.
- [41] Maki DG, Tambyah PA. Engineering out the risk for infection with urinary catheters. *Emerg Infect Dis* 2001;7:342-7.
- [42] Falagas ME, Athanasiou S, Iavazzo C, et al. Urinary tract infections after pelvic floor gynecological surgery: prevalence and effect of antimicrobial prophylaxis. A systematic review. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19(8):1165–1172.

- [43] Estelle Payerne, Debi Bhattacharya. Identifying the factors that influence patient acceptability of oral medicines: a systematic review of literature. PROSPERO 2013 CRD42013004033 Available from: [http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42013004033](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42013004033)
- [44] "Hiprex (Methenamine Hippurate) FDA Package Insert & Drug Facts." *Iodine*, [www.iodine.com/drug/hiprex/fda-package-insert](http://www.iodine.com/drug/hiprex/fda-package-insert).
- [45] "Calcium Carbonate Oral : Uses, Side Effects, Interactions, Pictures, Warnings & Dosing." *WebMD*, WebMD, [www.webmd.com/drugs/2/drug-579-139/calcium-carbonate-oral/calcium-supplements-oral/details](http://www.webmd.com/drugs/2/drug-579-139/calcium-carbonate-oral/calcium-supplements-oral/details).
- [46] "TheraCran Side Effects in Detail." *Drugs.com*, Drugs.com, [www.drugs.com/sfx/theracran-side-effects.html](http://www.drugs.com/sfx/theracran-side-effects.html).
- [47] Paeng, Christine H., et al. "Interaction Between Warfarin and Cranberry Juice." *Clinical Therapeutics*, vol. 29, no. 8, 2007, pp. 1730–1735., doi:10.1016/j.clinthera.2007.08.018.
- [48] Brubaker, Linda, et al. "American Urogynecologic Society Best-Practice Statement." *Female Pelvic Medicine & Reconstructive Surgery*, 2018, p. 1., doi:10.1097/spv.0000000000000550.