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Natural Approaches for Controlling Urinary Tract Infections

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1. Introduction

Urinary Tract Infections (UTIs) account for nearly 8 million physician visits and 1.5 million visits to emergency rooms annually in the United States (Foxman, 2003; Litwin et al., 2005; Stamm and Hooton, 1993). It is the second most common infection of any organ and is one of the most common infections in humans (Tabiban et al., 2008). UTIs account for a total annual cost of more than $ 3.5 billion in the United States (Litwin et al., 2005). UTI refers to the presence of clinical signs and symptoms arising from the genitourinary tract associated with the presence of one or more microorganisms (Guay, 2009). UTIs are usually localized to the bladder, kidneys or prostate. The term UTI in this chapter refers to infections of the lower urinary tract that involve the bladder and urethra. *Escherichia coli* is the predominant uropathogen responsible for roughly 80% of all UTI cases, followed by *Staphylococcus*, *Klebsiella*, *Enterobacter*, *Proteus* and *Enterococci* species (Ronald, 2003).

There are several approaches to the treatment and management of UTIs. Accurate classification of cases is the foremost and critical step in the clinical management of UTIs. UTIs may be primarily distinguished between the two anatomic locations of the infection, namely upper and lower tract infections. In majority of cases, the infection is associated with the lower part of the tract (Najar et al., 2009). Additionally, the infection may also be classified as complicated and uncomplicated based on the level of tissue involvement. Uncomplicated infections engross an episode of cysto-urethritis associated with bacterial colonization of the ureteral and bladder mucosa. Complicated infections involve pyelonephritis or prostitis and often occur as a result of obstruction or instrumentation in the tract (Huland and Busch, 1984; Najar et al., 2009). UTIs may also be classified as recurrent infection, reinfection or relapse (Najar et al., 2009). Reinfection is recurring infection due to a different microorganism that is usually drug susceptible, whereas relapse is a return of infection due to the same microorganism which is drug resistant. A relapse implies that there has been a failure to eradicate the infection (Cattell, 1973).

Traditionally, the treatment of UTIs consists of antimicrobial therapy administered in a regimen appropriate to the clinical situation, freqently administered temporally either as a prophylactic to reduce the risk of UTI or as a therapeutic approach. Several antibiotics such as penicillins, sulfanilamide, nitrofurantoin and cephalexin have been used in therapy (Nicolle, 2002). The customary UTI treatment involves a short course of antimicrobials such as a 3-day regimen of trimethorpim-sulfamethoxazole combination (Nickel, 2005a). This

initial therapy is based on knowledge of the predominant pathogens and their antimicrobial susceptibility (Perez-Lopez et al., 2009). Besides the therapeutic approach, preventive treatment with antibiotics are also administered to susceptible populations, including the elderly, children and women with recurrent UTIs. However, one major drawback to the use of antibiotics is the potential for development of antibiotic resistance among uropathogens (Head et al., 2008). The increasing prevalence of antibiotic resistant bacteria, escalating costs of antibiotic therapy and unsatisfactory therapeutic alternatives in recurrent UTIs have stimulated an interest in novel, non-antibiotic based methods for preventing and controlling UTIs (Vaughan, 2007; Smith et al., 2006).

2. Alternative treatment options

UTIs have been a common illness in humans long before bacteria were recognized as the causative agents. Initial therapy for UTIs was primarily the use of herbal treatments to ameliorate urinary symptoms, as recorded in the Ebers papyrus from ancient Egypt (Nickel, 2005b). The early 19th century provided detailed descriptions of UTIs with treatment that included hospitalization, bed rest, attention to diet, plastics, narcotics, herbal enemas, douches and surgery for stones, abscess and retention (Nickel, 2005b). However, with the advent of modern medicine, the use of select antibacterial agents and antibiotics for the treatment of UTIs was put into practice. Although the effectiveness of antibiotics was validated in clinical practice, the continued use of select agents in the prophylaxis and therapy of UTIs led to the emergence of antibiotic resistant uropathogens (Nickel, 2005c). This triggered an interest in the application of alternative, non-antibiotic approaches for preventing and controlling UTIs. This chapter discusses the various alternative approaches that are currently available and are being evaluated to control UTIs. These include the use of plant derived antimicrobials, probiotics, and vaccines targeting specific proteins in uropathogens.

2.1 Plant derived antimicrobials

Historically, plants have served as a basis for development of novel drugs, thereby contributing to human health and well-being. A variety of plant-derived polyphenols serve as dietary constituents as well as active components in a number of herbal and traditional medicines (Wollenweber, 1988). In excess of 5000 plant polyphenols have been identified, and several of them exhibit a wide spectrum of biological effects, including anti-inflammatory, antimicrobial, and anti-carcinogenic properties (Beretz et al., 1978). Several of them have been also used in the treatment and control of UTIs. These include cranberry, blueberry, berberine, bearberry, cinnamon and other herbs. Since several plant antimicrobials contain different functional groups in their structure, their antimicrobial activity is attributed to multiple mechanisms (Burt, 2004). Therefore, unlike antibiotics, the potential for bacteria to develop resistance to plant antimicrobials is relatively smaller (Ohno et al., 2003).

2.1.1 *Vaccinium macrocarpon* (Cranberry)

A significant body of literature exists on the positive effects of dietary intake of berry fruits on human health, performance and disease (Seeram, 2008). The ripe fruit of the cranberry is the part of the plant that is most commonly used for medicinal purposes. Cranberries are composed of 80-88% water and approximately 10% carbohydrates. Flavanoids,

anthocyanins, catechin, triterpenoids, organic acids and ascorbic acid are the other constituents that make up the rest of the 10% (Siciliano, 1996; Raz et al., 2004). Cranberry products such as the juice and tablets have been used as an alternative medicine to prevent UTIs in humans for decades.

Clinical and epidemiological studies support the use of cranberry in maintaining a healthy urinary tract (Perez-Lopez et al., 2009). The first controlled clinical trial demonstrating the use of cranberry juice in reducing the presence of bacteria in urine was conducted by Avorn and others (1994). This study included 192 participants, where baseline urine samples, followed by monthly samples were collected over a six month period, during which participants regularly consumed 300 ml of cranberry juice daily. The results of this study revealed that bacteriuria and pyuria occurred in 28% of the placebo group in comparison to only 14% in the cranberry juice group. Following this initial study, there have been several other investigations that demonstrated the antimicrobial property of cranberries against uropathogens. Although several studies have tested the antimicrobial effect of cranberries against multiple uropathogens, it was found to be most effective against uropathogenic *E. coli* (UPEC).

Di Martino et al (2005) investigated the effect of cranberry juice on UPEC biofilm population in a small group of human subjects. Similarly, Bailey et al (2007) conducted a study in women with recurrent UTI to evaluate the effects of a daily dose of concentrated cranberry extracts for a period of 12 weeks. In another study conducted by Bohbot (2007), a comparison was made between the use of proanthocyanidins (PAC) and cranberry total components. The results of the study demonstrated that components other than PAC also contribute to the UTI preventive effect of cranberries.

No definitive mechanism of action has been identified to explain the antimicrobial effect of cranberries against uropathogens. The initial hypothesis suggested that cranberry acidity produces the antibacterial effect in the body, but it was later disproved (Blatherwick and Long, 1923). Cranberries exert anti-adhesive effects on certain uropathogens (Ohnishi et al., 2006) and this effect is specific to certain components of cranberry (Ofek et al., 1991). Cranberries contain three different flavonoids (flavonols, anthocyanins and PAC), catechins, hydroxycinnamic and other phenolic acids and triterpenoids. The anthocyanins are absorbed in the human circulatory system and transported without any chemical change to the urine (Perez-Lopez et al., 2009). Cranberry products do not inhibit bacterial growth, but inhibit bacterial adherence to uroepithelial cells, thereby reducing the development of UTI. The anti-adhesive effects of p-fimbriated UPEC to uroepithelial cells are related to A-linked PAC as compared with lack of anti-adhesion activities of B-linked PAC from grape, apple juice, green tea and chocolate (Howell et al., 2005). The A-type PAC in cranberries enhance the anti-adhesive effects *in vitro* and in urine. PAC binds to lipopolysaccharide in gram negative bacteria. When *E. coli* was grown in the presence of cranberry components, the bacterial morphology changed to a more spherical cell-like form. These changes cause them to be repelled by the human cells (Liu et al., 2006).

Lavigne et al (2008) investigated the effect of cranberry capsules on bacterial adherence to urinary tract. Participants who consumed cranberry capsules showed a significant dose-dependent reduction in bacterial adherence to urinary epithelial cells compared to placebo. Another potential mechanism of action of cranberry against UPEC is the non-enzymatic generation of nitric oxide under mildly acidic conditions (MacMiking et al., 1997). Nitric oxide possesses potent antimicrobial activities that are both time and dose-dependent.

Although, cranberry has demonstrated potential against UTIs, dose administration recommendations of cranberry products have been poorly defined (Perez-Lopez et al., 2009). Available products include sweetened cranberry juice (OceanSpray®), which is 25% pure juice. Recommended doses vary from 4 to 32 oz/day. Recommended doses of the dried concentrated juice range from 600 to greater than 1200 mg/day (Ross, 2006; Lynch, 2004).
Cranberry has undergone extensive evaluation in the management of UTIs. Currently, there is no evidence that cranberry can be used to treat UTIs. Hence, the focus has been on its use as a prophylactic agent in the prevention of UTIs (Guay, 2009). The consumption of cranberry juice can help to prevent the adhesion of UPEC to the uroepithelium and thereby help reduce the incidence of UTIs. With rising concerns of antibiotic resistance among UPEC, cranberry could serve as an effective alternative in controlling UTIs.

2.1.2 *Vaccinium myrtillus* (Bilberry; Blueberry)

Blueberry extracts possess constituents similar to that found in cranberry extracts. Although extensive studies have not been performed on the antimicrobial effects of blueberry extracts, evidence indicates that blueberry extracts possess similar anti-adhesive effects against uropathogenic bacteria (Head, 2008). When compared to other fruit extracts such as guava, mango, orange, grapefruit or pineapple, blueberry constituents were reported to bind to the same uroepithelial cells where bacteria attach (Ofek et al., 1991; 1996). These studies demonstrated that the constituents in blueberry extracts like those in cranberry inhibited UPEC from adhering to the uroepithelial cells using the mannose-resistant adhesins. Similarly, Weiss et al (2002), compared the effect of cranberry, mango, melon, peach, plum and raspberry extracts on the ability of oral bacteria to aggregate and colonize the oral mucosa. It was found that only members of the *Vaccinium* genus were able to inhibit the bacterial aggregation. Cranberry extract was found to be most effective followed by blueberry, thus suggesting that blueberry may also serve as an alternative to the use of antibiotics in preventing UTIs.

2.1.3 Berberine

Berberine is an alkaloid present in many plants, including *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry) and *Berberis aristata* (tree turmeric). Berberine is present in the root, rhizome, and stem bark of the plants. Berberine extracts have been shown to be effective against a variety of organisms, including bacteria, viruses, fungi, protozoans, helminthes and Chlamydia (Head, 2008). Research using berberine demonstrated its inhibitory effect on the growth of several bacterial pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, , *E. coli, and Bacillus subtilis* (Cernakova and Kostalova, 2002). Supporting this finding, another study revealed that alkaloids from *Hydrastis* sp. possessed antibacterial activity against *E. coli*, *S. aureus* and *P. aeruginosa* (Scazzocchio et al., 2001). The antimicrobial effect of the ingredient alkaloids in the order of potency was berberine > coptisine > palmatine (Yan et al., 2008). Although the mechanisms behind antimicrobial property of berbine is not completely understood, it was reported to target the FtsZ protein involved in the first stage of bacterial cell division (Domadia et al., 2008).
In controlling UTIs, the antibacterial effect of berberine was attributed to its ability to inhibit bacterial adhesion to uroepithelial cells. Sun et al (1988a) demonstrated that growth of clinical isolates of *E. coli* in the presence of berberine sulfate completely inhibited fimbrial

synthesis. Likewise, berberine sulfate was found to inhibit the capacity of *Streptococcus pyogenes* to adhere to host cells (Sun et al., 1988b). Since *E. coli* infection in the urinary tract has been attributed to the migration of the pathogen from the gut, a reduction of *E. coli* load in the gut can indirectly reduce UTIs (Rabbani et al., 1987). In this context, berberine has been demonstrated to reduce *E. coli* induced diarrhea in human and animal subjects through its anti-secretory effects, thereby reducing the likelihood of bacterial migration into the urinary tract (Sach and Froehlich, 1982).

2.1.4 *Arctostaphylos uva ursi* (Bearberry)

This is another fruit commonly used for its antimicrobial property in controlling UTIs (Head, 2008). The active antimicrobial ingredient in bearberry is an aglycone hydroquinone which is released in alkaline urine (Uva ursi, 2004). A study conducted by Schindler et al (2002) involving human subjects who consumed a dried leaf extract of uva ursi showed that 64.8% of arbutin consumed in tablet form and 66.7% of arbutin ingested in aqueous solution were released in the urine. This significant level of the fruit extract in urine was attributed to its antimicrobial effect. Frohne (1970) and Kedzia et al (1975) conducted clinical studies with human subjects in which urine from patients given extracts of uva ursi or isolated arbutin was evaluated. The urine from the treatment group demonstrated significant antimicrobial activity against *E. coli*, *P. mirabilis*, *P. aeruginosa*, *S. aureus* and 70 other urinary bacteria. Frohne (1970) also demonstrated that the crude extract of uva ursi was more effective against bacteria than arbutin by itself. The one and only clinical study to investigate the effect of uva ursi in controlling UTIs was conducted by Larsson et al (1993). This study involved 57 women with chronic UTIs who were assigned to uva ursi extract or placebo for a period of one month and subsequently followed for a year. A statistically significant reduction in the incidence of UTIs was noted in the treatment group when compared to that in the placebo group, thereby demonstrating its efficacy as an antimicrobial against UTIs. The antimicrobial activity of uva ursi was attributed to its ability to change microbial cell surface characteristics. Supporting this, a study by Turi et al (1997) demonstrated that growth of clinical isolates of *E. coli* in the presence of uva ursi extracts increased the microbial cell surface hydrophobicity, thereby decreasing their ability to adhere to host cells. Additionally, uva ursi has diuretic and anti-inflammatory effects that indirectly aid in its use as an antimicrobial to control UTIs (Beaux et al., 1999; Kubo et al., 1990).

2.1.5 Trans-cinnamaldehyde

Trans-cinnamaldehyde (TC) is a major component of the bark extract of cinnamon (Adams et al., 2004). It is a generally recognized as safe (GRAS) molecule approved for use in foods by the Food and Drug Administration (FDA). The U. S. Flavoring Extract Manufacturers' Association reported that TC has a wide margin of safety between conservative estimates of intake and no observed adverse effect levels, from sub-chronic and chronic studies (Adams *et al*., 2004). The report also indicated no genotoxic or mutagenic effects due to TC. The antibacterial activity of TC against *Clostridium botulinum* (Bowles and Miller, 1993), *S. aureus* (Bowles *et al*., 1995), *E. coli* O157:H7 and *Salmonella* Typhimurium (Helander *et al*., 1998) has been previously reported. Although, cinnamon or cinnamon oil has been used for ages in the treatment of UTIs, no scientific study was undertaken to investigate its antimicrobial efficacy against uropathogens. Amalaradjou et al (2010) were the first to demonstrate the ability of trans-cinnamaldehyde to inactivate and inhibit UPEC biofilm formation on urinary

catheters. A follow up study conducted by the same group (Amalaradjou et al., 2011) indicated that trans-cinnamaldehyde inhibited the adhesion and invasion of uroepithelial cells by UPEC by downregulating major virulence genes in the pathogen. These results indicate the potential use of trans-cinnamaldehyde as an antimicrobial for controlling UTIs.
The antimicrobial effect of TC could be attributed to multiple mechanisms. A critical property of essential oils or their components, including TC is their hydrophobicity, which helps them to target the lipid-containing bacterial cell membrane and mitochondria (Sikkema et al., 1994). This makes these membranes more permeable, leading to leakage of ions and other cell contents. In addition to the effect on cell membranes, TC is also believed to kill bacteria by inhibiting energy generation and glucose uptake (Gill and Holey, 2006). Yet another mechanism by which cinnamon oil and its components kill microorganisms is by their inhibitory effect on enzymes such as amino acid decarboxylases (Wendakoon and Sakaguchi, 1995). It is also known that plant essential oils and their components, including that from cinnamon are capable of inhibiting the production of virulence factors, and modulating bacterial pathogenesis (Smith-Palmer et al., 2002). For example, Smith-Palmer and coworkers (2004) reported that sub-inhibitory concentrations of oils of cinnamon, bay, clove and thyme significantly decreased the production of enterotoxin A and α-toxin, two virulence factors in *S aureus*. The authors concluded that since the essentials oils did not directly inactivate or prevent export of α-toxin from the cells, their inhibitory activity could be at the transcriptional or translational level. Similarly, low concentrations of cinnamaldehyde were reported to inhibit quorum sensing (QS) or cell-density dependent regulation of gene expression in *E. coli* and biofilm synthesis in *Vibrio* spp. without inhibiting bacterial growth (Brackman et al., 2008). Amalaradjou et al (2011) demonstrated that trans-cinnamaldehyde reduced the expression of several virulence genes essential for UPEC motility, host cell attachment and invasion. Thus, the ability of trans-cinnamaldehyde to inhibit bacteria through multipronged mechanisms makes it a potential candidate for use as an antimicrobial agent for controlling UTIs.

2.1.6 Other herbs

Essential oil extracted from *Salvia officinalis* (Garden sage; common sage) has been shown to be inhibitory against several uropathogens obtained from the urine samples of individuals with UTIs. Sage oil completely inhibited several pathogens, including *Klebsiella*, *Enterobacter* species, *E. coli* , *Proteus mirabilis* and *Morganella morganii* (Pereira et al., 2004). *Barosma betulina* (bachu) is another herb which has been used in the treatment of urinary tract infection, catarrhal cystitis and urethritis for a long time (Barnes et al., 2007). *In vitro* studies have demonstrated its antimicrobial effect against uropathogens (Mills and Bone, 2000). In addition to its antimicrobial effect, bachu also has diuretic properties (Simpson, 1998). Several other herbs that are used for the treatment of UTIs but lack scientific basis include *Agrimonia eupatoria* (agrimony), *Althea officinalis* (marshmallow), *Apium graveolens* (celery seed), *Arctium lappa* (burdock), *Elymus repens* (couchgrass), *Hydrangea aborescens* (hydrangea), *Juniperus communis* (juniper), *Mentha piperita* (peppermint), *Taraxacum officinalis* leaf (dandelion), *Ulmus fulva* (slippery elm) and *Zea mays* (corn silk).

2.2 Dietary interventions

Besides the use of antimicrobials, several nutrients have been used in the management, prevention and treatment of UTIs. These include vitamins, salts, and sugars.

2.2.1 Vitamins

Ochoa et al (2007) investigated the efficacy of vitamin C for its effect on UTIs in pregnant women. The study consisted of 110 pregnant women who were divided into two groups. One group received a dose of 100 mg vitamin C daily while the other group was used as a control for a period of three months. Urine sample was collected from the subjects and evaluated for presence of uropathogens. The results of this study revealed that the vitamin C group had a significantly lower incidence of UTIs than the control group. Similarly, the use of vitamin A in the management of UTIs in children was evaluated by Yilmaz et al (2007). This study tested 24 children, 12 in the vitamin A group who received 200,000 IU of vitamin A, in addition to antimicrobial therapy for 10 days and 12 in the control group who just received the antimicrobial. The subjects were followed for one year and continued on antibiotic prophylaxis. It was observed that the children in the vitamin A group had a significantly lower incidence of UTIs than the control group.

2.2.2 Citrate salts

The purpose behind the use of citrate salts in the management of UTIs is to alkalinize the urine, since alkaline urine can provide significant benefit for UTI symptoms such as dysuria. In a study conducted by Spooner (1984), it was shown that intake of sodium citrate in women with UTI for a period of 48 hours significantly improved symptoms in 80 percent of the subjects with bacteriuria. In addition to improving symptoms like dysuria, alkalinity in the urine aids to provide an effective environment for certain antimicrobials such as uva ursi and berberine to function (Head, 2008). Potassium and sodium citrate have also been found to be effective against urinary candidiasis, a mold infection associated with the presence of indwelling catheters. Strassner and Friesen (1995), in a clinical study with hospitalized patients, demonstrated that oral intake of potassium-sodium-hydrogen-citrate for a period of two days to one month resulted in a significant increase in urinary pH and simultaneous disappearance of Candida in the urine.

2.2.3 D- mannose

Simple sugars like D-mannose prevent adherence of bacteria to uroepithelial cells. Ofek and Beachey (1978) identified a mannose-specific lectin on the surface of adherent strains of *E. coli*. Mannose functions as the primary bladder cell receptor site for UPEC to bind. Likewise, Hung et al (2002) reported that the first step in the adhesion of UPEC to the uroepithelial cells is the binding of FimH adhesin to the bladder epithelium via interaction with mannose moieties on the host cell surface. Thus the use of mannose or mannose analogs can help to block adhesion of *E. coli* to the bladder epithelium.

Several studies have also investigated the efficacy of alpha-glycosides of mannose and D-mannose in controlling UTIs (Firon et al., 1987; Schaeffer et al., 1984). An *in vivo* study conducted in mouse demonstrated that D-mannose not only blocked adhesion of *E. coli* to the urinary tract epithelium, but also prevented bacterial invasion and subsequent biofilm formation (Wellens et al., 2008). Growth of *E. coli* strains isolated from women with recurrent UTIs in the presence of D-mannose inhibited the adherence of *E. coli* by 42% (Schaffer et al., 1984). Similarly in a study of urinary tract epithelial cells collected from voided urine of healthy women, use of a 2.5% solution of D-mannose, D- mannitol or alpha-methyl-D-mannoside completely inhibited *E. coli* adherence to the uroepithelium. However, when a similar concentration of D-lyxose, D-arabinose, D-fructose and D-glyceraldehyde

were used, only a partial inhibition of bacterial adhesion was noticed. Additionally, the use of lower concentrations (0.1-1.0%) of mannose, mannitol and mannoside also resulted in a partial inhibition of bacterial adhesion to urinary tract epithelial cells (Schaffer et al., 1980).
In addition to the use of naturally existing mannose residues and its derivatives in the control of UTIs, Klein et al (2010) synthesized and evaluated the efficacy of several mannosides in blocking bacterial-host interaction. Among the different mannosides developed and evaluated using a mouse UTI model, para substituted biphenyl derivative of D-mannose was found to be the most effective in controlling UTIs. Following oral administration of this mannoside, bacterial numbers were reduced by 2 orders and 4 orders of magnitude in the urine and bladder, respectively. This FimH antagonist thus provides an alternative approach with a new class of orally available antimicrobials for effective treatment of UTIs.

2.3 Probiotics

Probiotics are live organisms which when administered in adequate amounts confer a health benefit on the host (FAO/WHO, 2001). The rationale for the use of probiotics is based on the gastrointestinal and genitourinary regulatory role played by the commensal microflora, and the need for restoration of this microbial ecosystem after an imbalance or infection (Barrons and Tassone, 2008). For use as a probiotic in controlling UTIs, the candidate culture must exhibit adequate antibacterial properties. For example, an important attribute of an ideal probiotic culture such as lactobacilli is the ability to maintain a low pH ≤ 4.5, where the acidic environment provides lactobacilli a favorable environment to multiply and produce additional antibacterial molecules, including bacteriocin and hydrogen peroxide (Aroutcheva et al., 2001). In a study investigating the defense factors against infection in 22 lactobacilli strains isolated from healthy human vaginal ecosystems, moderate to high production of hydrogen peroxide and bacteriocin was observed in 82% and 68% of the strains (Aroutcheva et al., 2001).
Besides their ability to produce acid, hydrogen peroxide and bacteriocins, lactobacilli may also offer protection against UTIs through the production of biosurfactants. Biosurfactants inhibit growth of uropathogens by inhibiting the adhesion of these pathogens to the uroepithelium (Velraeds et al., 1996). A study conducted using 15 strains of lactobacilli showed that the strains produced varying amounts of biosurfactants providing up to 82% inhibition of *Enterococcus fecalis* adhesion to a glass surface (Velraeds et al., 1996). Moreover, lactobacilli co-aggregate with uropathogens to block their adhesion and/or displace previously adherent uropathogens from the urinary tract. This co-aggregation can create a microenvironment in which the inhibitory substances produced by the lactobacilli can concentrate on the pathogens and inhibit them (Mastromarino et al., 2002).
Osset et al (2001) conducted an *in vitro* study in which the antimicrobial ability of 15 *Lactobacillus* species against pathogens was investigated. *Lactobacillus crispatus* was found to be the species that demonstrated the strongest ability to block pathogen adhesion. Another *in vitro* study examined the antagonistic effect of five probiotic species against six pathogenic bacteria. The results revealed that a pyelonephritic *E. coli* strain was sensitive to *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* Bb 12 and *Bifidobacterium longus* 46 (Hutt et al., 2006).
Several clinical studies have investigated the effect of probiotic suppositories for the prevention of UTIs. Reid et al (1992) investigated the effect of probiotic lactobacill in controlling infection in women with acute UTIs (Reid et al., 1995). These patients were

treated with antibiotics for three days and recurrence occurred in 41% of the patients. These individuals were randomly assigned to Lactobacillus suppositories or placebo suppositories twice weekly for two weeks, then once a month for the next two months. Recurrence was 21 percent in the Lactobacillus group compared to 47% in the placebo group. The same group of researchers conducted a follow-up study comparing the effects of suppositories containing the Lactobacillus species with suppositories containing Lactobacillus growth factor. The subjects were administered with either one of the suppositories once weekly for 12 months. At the end of the 12 months, both the groups exhibited a 73% reduction in the incidence of UTIs (Reid et al., 1995).

Studies were also conducted to evaluate the efficacy of oral probiotics in controlling UTIs. In order for an oral probiotic to be effective, it must be able to colonize the intestinal and/or urogenital region. *L. rhamonosus* GR-1 and *L. fermentum* RC-14 were administered twice daily for 14 days and the bacterial recovery from the vaginal tissue was monitored (Reid et al., 2001). It was observed that the vaginal epithelium was colonized with lactobacilli within one week of the oral administration (Reid et al., 2001). Similarly studies in pediatric populations revealed that administration of *L. rhamnosus* GG orally for 50 days resulted in a reduction in UTI incidence rate compared to the placebo group (Dani et al., 2002). Taken together, results from these aforementioned studies suggest the potential benefit of probiotics in controlling UTIs.

2.4 Hormone therapy

In postmenopausal women, hormone waning results in thinning of the vaginal and urethral mucosa, disruption of the normal vaginal flora and an increased risk for UTIs (Head, 2008). Therefore administration of estrogen in such patients has been reported to reduce UTIs. A randomized study including postmenopausal women evaluated the effect of intravaginally administered estriol in reducing UTIs. The results of this study showed a significant reduction in the incidence of UTIs compared to the placebo group. It was also observed that Lactobacilli that were absent in the vaginal cultures of subjects at the beginning of the trial reappeared in 61 percent of the estriol group (Raz and Stamm, 1993).

2.5 Vaccines

As with other infectious diseases, UTIs can also be controlled using vaccines. Wieser et al.(2010) reported that an ideal vaccine target against uropathogens should be (i) exposed on the bacterial surface and (ii) widely distributed among clinical isolates but not among commensal strains of the gut flora, (iii) possess epitopes that are conserved across diverse strains, and (iv) elicit a protective immune response. Additional desirable characteristics of an effective vaccine target include increased expression at the site of infection and a role in the pathogenesis of disease (Wieser et al., 2010).

Several studies have investigated the use of potential antigens as targets for vaccine development against UPEC. Initial studies for vaccine candidates consisted of single target protein or whole cells. Langermann et al (1997) evaluated the use of an adhesion based vaccine targeting the FimH protein on the surface of UPEC. Immunization with FimH reduced *in vivo* bacterial colonization of the bladder mucosa by more than 99 percent in a murine cystitis model, and immunoglobulin G to FimH was detected in the urinary samples from protected mice. Additionally, passive systemic administration of immune sera to FimH

also resulted in reduced bladder colonization by UPEC. A similar study by Li et al (2004) developed an intranasal vaccine against *Proteus mirabilis* infections in the urinary tract. The mice were vaccinated with formalin-killed bacteria or purified mannose-resistant Proteus-like fimbriae (MR/P), a surface antigen expressed by *P. mirabilis* during UTI. Four different routes of administration, including subcutaneous, intradermal, intranasal and trans urethral were evaluated in this study, where intranasal administration of MR/P elicited the most protective immune response against *P. mirabilis* UTI.

Alteri et al (2009) investigated the use of six novel vaccine candidates against UPEC. These candidates were indentified using bioinformatics, functional genomics, transcriptomic and proteomic analyses. All the six proteins belonged to the class of outer membrane iron receptors that are upregulated in an iron restricted environment. Intranasal administration of these antigens in mice elicited both systemic and mucosal immune responses that included the production of antigen-specific IgM, IgG and IgA antibodies, cytokine responses and protection against UTI in the mouse model (Alteri et al., 2009). A similar study was also conducted by Wieser et al (2010), where they evaluated the use of a subunit vaccine against extra intestinal *E. coli*. Using a novel approach of computer-aided design, two completely artificial genes were created, both encoding eight peptide domains derived from these extra intestinal *E. coli* proteins. In mice, the vaccine was highly immunogenic, eliciting both strong humoral and cellular immune responses. Nasal application of the vaccine resulted in high secretory immunoglobulin A (sIgA) production, which was detectable on the mucosal surface of the urogenital tract. Finally, it bestowed protection, as shown by a significant reduction of bacterial load in a mouse model of extra intestinal *E. coli* peritonitis.

Besides the use of immunogenic antigens as vaccines, immunotherapy for UTIs can also be accomplished using immunomodulants. A study carried by Krcmery et al (2010) investigated the efficacy of two immunomodulatory agents (Urovaxom and luivac) for the management of recurrent UTIs in women over a 12 month period. The results indicated that a combined treatment using immunotherapy and chemoprophylaxis significantly reduced the occurrences of UTI relapses in these women.

3. Conclusion

Infections of the genitourinary tract are common occurrences in individuals especially in young women, during pregnancy and in post menopausal women. The conventional use of antibiotics in the prevention and treatment of acute and chronic recurring infections contribute to gut and vaginal dysbiosis and bacterial antibiotic resistance. In an attempt to control the increasing trends in infections with antibiotic resistant uropathogens, there is a renewed interest in the use of non-antibiotic based intervention strategies against UTIs. Several studies have investigated the use of natural substances in the prevention and treatment of UTIs. Nutrients and botanicals such as cranberry, berberine, cinnamaldehyde, probiotics and vaccines have demonstrated the greatest effectiveness. While most clinical research has evaluated the antimicrobial potential of these natural substances, their mechanism of action and the clinical experience of health care practitioners are critical for evaluating their effectiveness (Head, 2008). Use of these alternatives in the control of UTIs would help to circumvent dysbiosis and microbial drug resistance induced by the repeated use of antibiotics.

4. References

Adams, T. B., Cohen, S. M., Doull, J., Feron, V. J., Goodman, J. I., Marnett, L. J., Munro, I, C., Portoghese, P. S. Smith, R. L., Waddell, W. J. & Wagner, B. M. (2004). The FEMA GRAS assessment of cinnamyl derivatives used as flavor ingredients. *Food Chemistry and Toxicology*, Vol. 42, No. 2,(February 2004), pp.157-185 ISSN 0278-6915

Alteri, C. J., Hagan, E. C., Sivick, K. E., Smith, S. N. & Mobley, H. L. (2009). Mucosal immunization with iron receptor antigens protects against urinary tract infection. *PLoS Pathog*, Vol. 5, No. 9, (September 2009), pp.e1000586 ISSN 1553-7374

Amalaradjou, M. A., Narayanan, A. & Venkitanarayanan, K. 2011. Trans-cinnamaldehyde decreases attachment and invasion of uropathogenic *Escherichia coli* in urinary tract epithelial cells by modulating virulence gene expression. J Urol, Vol. 185, No. 4, (April 2011), pp.1526-1531 ISSN 0022-5347

Amalaradjou, M. A., Narayanan, A., Baskaran, S. A. & Venkitanarayanan, K. 2010. Antibiofilm effect of trans-cinnamaldehyde on uropathogenic *Escherichia coli*. *J Urol*, Vol. 184, No. 1, (July 2010), pp.358-363 ISSN 0022-5347

Aroutcheva, A., Gariti, D., Simon, M., Shott, S., Faro, J., Simoes, J. A., Gurguis, A. & Faro, S. (2001). Defense factors of vaginal Lactobacilli. *Am J Obstet Gynecol*, Vol. 185, No. 2, (August 2001), pp.375-379 ISSN 0002-9378

Avorn, J., Monane, M., Gurwitz, J. H., Glynn, R. J., Choodnovskiy, I. & Lipsitz, L. A. (1994). Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA*, Vol. 271, No. 10, (March 1994), pp. 751-754 ISSN *0098-7484*

Bailey, D. T., Dalton, C., Joseph Daugherty, F. & Tempesta, M. S. (2007). Can a concentrated cranberry extract prevent recurrent urinary tract infections in women? A pilot study. *Phytomedicine*, Vol. 14, No. 4, (April 2007), pp. 237-241 ISSN 0944-7113

Barnes, J., Anderson, L. A. & Phillipson, J. D. (2007). *Herbal Medicines*. 3rd ed. Grayslake, IL: Pharmaceutical Press ISBN 0853696233

Barrons, R. & Tassone, D. (2008). Us eof Lactobacillus probiotics for bacterial genitourinary infections in women: A review. *Clinical Therapeutics*, Vol. 30, No. 3, (November 2008), pp.453-468 ISSN 0149-2918

Beaux, D., Fleurentin, J. & Mortier, F. (1999). Effect of extracts of *Orthosiphon stamineus Benth*, *Hieracium pilosella L.*, *Sambucus nigra L.* and *Arctostaphylos uva-ursi* (L.) Spreng. in rats. *Phytother Res*, Vol. 13, No. 3, (May 1999), pp.222-225 ISSN 0951-418X

Beretz, A., Anton, R. & Stoclet, J. C. (1978). Flavonoid compounds are potent inhibitors of cyclic AMP phosphodiesterase. *Experientia*, Vol. 34, No. 8, (August 1978) pp. 1054-1055 ISSN 0014-4754

Blatherwick, N. R. & Long, M. L. (1923). Studies of urinary acidity. II. The increased acidity produced by eating prunes and cranberries. *J Biol Chem*, Vol. 57, No. 3, (October 1923), pp. 815-818 ISSN 0021-9258

Bohbot, J. M. (2007). Resultas d'une etude randomisee en double aveugle sur la prevention des cystitis recidivants par GynDelta. *La Revue Pract Gynecol Obstetr*,No. 3, pp. 3-6 ISSN 0035-290X

Borchert, D., Sheridan, L., Papatsoris, A., Faruquz, Z., Barua, J. M., Junaid, I., Pati, Y., Chinegwundoh, F. & Buchholz, N. (2008). Prevention and treatment of urinary

tract infection with probiotics: Review and research perspective. *Indian J Urol*, Vol. 24, No. 2, (April 2008), pp. 139-144 ISSN 0970-1591

Bowles, B. L. & Miller, A. J. (1993). Antibotulinal properties of selected aromatic and aliphatic aldehydes. *J Food Prot*, Vol. 5, pp.788-794 ISSN 0362-028X

Bowles, B. L., Sackitey, S. K. & Williams, A. C. 1995. Inhibitory effects of flavor compounds on *Staphylococcus aureus* WRRC B124. Journal of Food Safety, Vol. 15, pp.337-347 ISSN 1745-4565

Brackman, G., Defoirdt, T., Miyamoto, C., Bossier, P., Van Calenbergh, S., Nelis, H. & Coenye. T. (2008). Cinnamaldehyde and cinnamaldehyde derivatives reduce virulence in *Vibrio* spp. by decreasing the DNA-binding activity of the quorum sensing response regulator LuxR. *BMC Microbiol*, Vol. 8, pp.149, ISSN 1471-2180

Burt, S. (2004). Essential oils: their antibacterial properties and potential applications in foods - a review. *Intl J Food Microbiol,* Vol. 94, No. 3, (August 2004), pp. 223-253 ISSN 0168-1605

Catell, W. R. (1973). The localization of urinary tract infection and its relationship to relapse, reinfection and treatment. IN. Brumfitt, W. & Asscher, A. W. *Urinary Tract Infection*. ISBN 0387901477, London: Oxford University Press; 1973. Pp. 206-214.

Cernáková, M. & Kostálová, D. (2002). Antimicrobial activity of berberine – a constituent of *Mahonia aquifolium*. *Folia Microbiol*, Vol. 47, No. 4, (August, 2002), pp. 375-378 ISSN 0015-5632

Dani, C., Biadaioli, R., Bertini, G., Martelli, E. & Rubaltelli, F. F. (2002). Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. *Biol Neonate*, Vol. 82, No. 2, (August 2002), pp.103-108 ISSN 0006-3126

Di Martino, P., Agniel, R., Gaillard, J. L. & Denys, P. (2005). Effects of cranberry juice on uropathogenic *Escherichia coli in vitro* biofilm formation. *J Chemother*, Vol. 17, No. 5, (October 2005), pp. 563-565 ISSN 1120-009X

Domadia PN, Bhunia A, Sivaraman J, Swarup S, Dasgupta D. (2008). Berberine targets assembly of *Escherichia coli* cell division protein FtsZ. *Biochemistry*, Vol. 47, No. 10, (March 2008), pp.3225-3234 ISSN *0006-2960*

FAO/WHO. (2001). Report of a joint FAO/WHO expert consultation on health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. American Cordoba Park Hotel, Cordoba, Argentina, 1-4 October 2001 http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf . Accessed April 02, 2010

Firon, N., Ashkenazi, S., Mirelman, D., Ofek, I. & Sharon, N. (1987). Aromatic alpha-glycosides of mannose are powerful inhibitors of the adherence of type 1 fimbriated *Escherichia coli* to yeast and intestinal epithelial cells. *Infect Immun*, Vol. 55, No. 2, (February 1987), pp.472-476 ISSN 0019-9567

Foxman, B. (2003). Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Dis. Mon*., Vol. 49, No. 2, (February 2003), pp. 53-70 ISSN 0011-5029

Frohne, D. (1970). The urinary disinfectant effect of extract from leaves uva ursi. *Planta Med*, Vol. 18, No. 1, (January 1970), pp. 1-25 ISSN 0032-0943

Gill, A. O. & Holley, R. A., 2006. Disruption of *Escherichia coli*, *Listeria monocytogenes* and *Lactobacillus sakei* cellular membranes by plant oil aromatics. *Int J Food Microbiol*, Vol. 108, pp.1-9 ISSN 0168-1605

Guay, D. R. P. (2009). Cranberry and urinary tract infections. *Drugs*, Vol. 69, No. 7, (May 2009), pp. 775-807 ISSN 0012-6667

Head, K. A. (2008). Natural approaches to prevention and treatment of the lower urinary tract. *Alternative Medicine Review*, Vol. 13, No. 3, (September 2008), pp. 227-244 ISSN 1089-5159

Helander, I. M., Alakomi, H. L., Latva-Kala, K., Mattila-Sandholm, Y., Pol, L., Smid, E. J., Gorris, L. G. M. & von Wright, A., 1998. Characterization of the action of selected essential oil components on gram-negative bacteria. *J Agric Food chem*, Vol. 46, pp.3590-3595 ISSN

Howell, A. B., Reed, J. D., Krueger, C. G., Winterbottom, R., Cunningham, D. G. & Leahy, M. (2005). A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. *Phytochemistry*, Vol. 66, No. 18, (September 2005), pp. 2281-2291 ISSN 0031-9422

Huland, H. & Busch, R. (1984). Pyelonephritic scarring in 213 patients with upper and lower urinary tract infections: long-term follow-up. *J Urol*, Vol. 139, No. 5, (November 1984), pp. 936-939 ISSN 0022-5347

Hung, C. S., Bouckaert, J., Hung, D., Pinkner, J., Widberg, C., DeFusco, A., Auguste, C. G., Strouse, R., Langermann, S., Waksman, G. & Hultgren, S. J. 2002. Structural basis of tropism of *Escherichia coli* to the bladder during urinary tract infection. *Mol Microbiol*, Vol. 44, No. 4, (May 2002), pp.903-915 ISSN 0950-382X

Hütt, P., Shchepetova, J., Lõivukene, K., Kullisaar, T. & Mikelsaar, M. (2006). Antagonistic activity of probiotic Lactobacilli and Bifidobacteria against entero- and uropathogens. *J Appl Microbiol*, Vol. 100, No. 6, (June 2006), pp.1324-1332 ISSN 1365-2672

Kedzia, B., Wrociński, T., Mrugasiewicz, K., Gorecki, P. & Grzewińska, H. (1975). Antibacterial action of urine containing products of arbutin metabolism. *Med Dosw Mikrobiol*, Vol. 27, No. 3, pp.305-314 ISSN 0025-8601

Klein, T., Abgottspon, D., Wittwer, M., Rabbani, .S, Herold, J., Jiang, X., Kleeb, S., Lüthi, C., Scharenberg, M., Bezençon, J., Gubler, E., Pang, L., Smiesko, M., Cutting, B., Schwardt, O. & Ernst, B. (2010). FimH antagonists for the oral treatment of urinary tract infections: from design and synthesis to in vitro and in vivo evaluation. *J Med Chem*, Vol. 53, No. 24, (December 2010), pp.8627-8641 ISSN *1520-4804*

Krcméry, S., Hromec, J., Gábrisová, Z. & Tahotný, R. (2010). Immunotherapy and long-term chemoprophylaxis in prevention of recurrent urinary infections in women. *Vnitr Lek*, Vol. 56, No. 9, (September 2010), pp.955-960 ISSN 0042-773X

Kubo, M., Ito, M., Nakata, H. & Matsuda, H. (1990). Pharmacological studies on leaf of *Arctostaphylos uva-ursi* (L.) Spreng. I. Combined effect of 50% methanolic extract from Arctostaphylos uva-ursi (L.) Spreng. (bearberry leaf) and prednisolone on immuno-inflammation. *Yakugaku Zasshi*, Vol. 110, No. 1, (January 1990), pp.59-67 ISSN 1347-5231

Langermann, S., Palaszynski, S., Barnhart, M., Auguste, G., Pinkner, J. S., Burlein, J., Barren, P., Koenig, S., Leath, S., Jones, C. H. & Hultgren, S. J. (1997). Prevention of mucosal *Escherichia coli* infection by FimH-adhesin-based systemic vaccination. *Science*, Vol. 276, No. 5312, (April 1997), pp.607-611 ISSN 0036-8075

Larsson, B., Jonasson, A. & Fianu, S. (1993). Prophylactic effect of UVA-E in women with recurrent cystitis: a preliminary report. *Curr Ther Res*, Vol. 53, No. 4, (July 1993), pp. 441-443 ISSN 0011-393X

Lavigne, J. P., Bourg, G., Combescure, C., Botto, H. & Sotto, A. (2008). In-vitro and in-vivo evidence of dose-dependent decrease of uropathogenic *Escherichia coli* virulence after consumption of commercial Vaccinium macrocarpon (cranberry) capsules. *Clin Microbiol Infect*, Vol. 14, No. 4, (April 2008), pp.350-355 ISSN 1198-743X

Li, X., Erbe, J. L., Lockatell, C. V., Johnson, D. E., Jobling, M. G., Holmes, R. K. & Mobley, H. L. (2004). Use of translational fusion of the MrpH fimbrial adhesin-binding domain with the cholera toxin A2 domain, coexpressed with the cholera toxin B subunit, as an intranasal vaccine to prevent experimental urinary tract infection by *Proteus mirabilis*. *Infect Immun*, Vol. 72, No. 12, (December 2004), pp.7306-7310 ISSN 0019-9567

Litwin, M. S., Saigal, C. S., Yano, E. M., Avila, C., Geschwind, S. A. & Hanley, J. M. (2005). Urologic diseases in America project: analytical methods and principal findings. *J. Urol*., Vol. 173, No. 3, (March 2005), pp. 933-937 ISSN 0022-5347

Liu, Y., Black, M. A., Caron, L. & Camesano, T. A.(2006). Role of cranberry juice on molecular-scale surface characteristics and adhesion behavior of *Escherichia coli*. *Biotechnol Bioeng*, Vol. 93, No. 2, (February 2006), pp. 297-305 ISSN *0006-3592*

Lynch, D. M. (2004). Cranberry for prevention of urinary tract infections. *Am Fam Physician*. Vol. 70, No. 11, (December 2004), pp.2175-2177 ISSN *0002-838X*

MacMicking, J., Xie, Q. W. & Nathan, C. (1997). Nitric Oxide and macrophage function. *Annu Rev Immunol*, Vol. 15, (April 1997), pp. 323-350 ISSN 0732-0582

Mastromarino, P., Brigidi, P., Macchia, S., Maggi, L., Pirovano, F., Trinchieri, V., Conte, U. & Matteuzz,i D. (2002). Characterization and selection of vaginal Lactobacillus strains for the preparation of vaginal tablets. *J Appl Microbiol*, Vol. 93, No. 5, (October 2002), pp.884-893 ISSN 1365-2672

Mills, S. & Bone. K. (2000). Buchu. In: *Principles and Practice phytotherapy: Mordern herbal medicine*. Churchill Livingstone, pp. 310-312 ISBN 0443060169

Najar, M. S., Saldanha, C. L. & Banday, K. A. (2009). Approach to urinary tract infections. *Indian J Nephrol*, Vol. 19, No. 4, (October 2009), pp. 129-139 ISSN 0971-4065

Nickel, J. C. (2005a). Practical management of recurrent urinary tract infections in premenopausal women. *Rev Urol*, Vol. 7, No. 1, (Winter), pp. 11-17 ISSN 1523-6161

Nickel, J. C. (2005b). Management of urinary tract infections: historical perspective and current strategies: part 1 – before antibiotics. *The Journal of Urology*, Vol. 173, No. 1, (January 2005), pp. 21-26 ISSN 0022-5347

Nickel, J. C. (2005c). Management of urinary tract infections: historical perspective and current strategies: part 2 – modern management. *The Journal of Urology*, Vol. 173, No. 1, (January 2005), pp. 27-32 ISSN 0022-5347

Nicolle, L. E. (2002). Urinary tract infection: traditional pharmacologic therapies. *Am J Med*, Vol. 113, No. 1A, (July 2002), pp. 35s-44s ISSN 0002-9343

Ochoa-Brust, G. J., Fernandez, A. R., Villanueva-Ruiz, G. J., Velasco, R., Trujillo-Hernández, B. & Vásquez, C. (2007). Daily intake of 100 mg ascorbic acid as urinary tract infection prophylactic agent during pregnancy. *Acta Obstet Gynecol Scand*, Vol. 86, No. 7, (July 2007), pp.783-787 ISSN 0300-8835

Ofek, I. & Beachey, E. H. (1978). Mannose binding and epithelial cell adherence of Escherichia coli. *Infect Immun*, Vol. 22, No. 1, (October 1978), 247-254 ISSN 0019-9567

Ofek, I., Godhar, J., Zafriri, D., Lis, H., Adar, R. & Sharon, N. (1991). Anti-*Escherichia coli* adhesion activity of cranberry and blueberry juices. *N Engl J Med*, Vol. 324, No. 22, (May 1991), pp. 1599 ISSN 0028-4793

Ofek, I., Goldhar, J. & Sharon, N. (1996). Anti-*Escherichia coli* adhesin activity of cranberry and blueberry juices. *Adv Exp Med Biol*, Vol. 408, pp.179-83 ISSN 0065-2598

Ohnishi, R., Ito, H., Kasajima, N., Kaneda, M., Kariyama, R., Kumon, H., Hatano, T. & Yoshida, T. (2006). Urinary excretion of anthocyanins in humans after cranberry juice ingestion. *Biosci Biotechnol Biochem*, Vol. 70, No. 7, (July 2006), pp. 1681-1687 ISSN 0916-8451

Ohno, T., Kita, M., Yamaoka, Y., Imamura, S., Yamamoto, T., Mitsufuji, S., Kodama, T., Kashima, K. & Imanishi, J. (2003). Antimicrobial activity of essential oils against *Helicobacter pylori*. *Helicobacter*, Vol. 8, No. 3, (June 2003), pp. 207-215 ISSN 1083-4389

Osset, J., Bartolomé, R. M., García, E. & Andreu, A. (2001). Assessment of the capacity of Lactobacillus to inhibit the growth of uropathogens and block their adhesion to vaginal epithelial cells. *J Infect Dis*, Vol. 183, No. 3, (February 2001), pp.485-491 ISSN 1553-6203

Pereira, R. S., Sumita, T. C., Furlan, M. R., Jorge, A. O. & Ueno, M. (2004). Antibacterial activity of essential oils on microorganisms isolated from urinary tract infection. *Rev Saude Publica*, Vol. 38, No. 2, (April 2004), pp.326-328 ISSN 0034-8910

Pérez-López, F. R., Haya, J. & Chedraui, P. (2009). Vaccinium macrocarpon: an interesting option for women with recurrent urinary tract infections and other health benefits. *J Obstet Gynaecol Res*, Vol. 35, No. 4, (August 2009), pp. 630-639 ISSN 1341-8076

Rabbani, G. H., Butler, T., Knight, J., Sanyal, S. C. & Alam, K. (1987). Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic *Escherichia coli* and *Vibrio cholerae*. *J Infect Dis*, Vol. 155, No. 5, (May 1987), pp.979-984 ISSN 0022-1899

Raz, R. & Stamm, W. E. (1993). A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*, Vol. 329, No. 11, (September 1993), pp.753-756 ISSN 0028-4793

Raz, R., Chazan, B. & Dan, M. (2004). Cranberry juice and urinary tract infection. *Clin Infect Dis*, Vol. 38, No. 10, (May 2004), pp. 1413-1419 ISSN 1058-4838

Reid, G., Bruce, A. W. & Taylor, M. (1992). Influence of three-day antimicrobial therapy and Lactobacillus vaginal suppositories on recurrence of urinary tract infections. *Clin Ther*, VOl. 14, No. 1, (January-February 1992), pp.11-16 ISSN 0149-2918

Reid, G., Bruce, A. W. & Taylor, M. (1995). Instillation of Lactobacillus and stimulation of indigenous organisms to prevent recurrence of urinary tract infections. *Microecol Ther*, Vol. 23, pp.32-45 ISSN 0720-0536

Reid, G., Beuerman, D., Heinemann, C. & Bruce, A. W. (2001). Probiotic Lactobacillus dose required to restore and maintain a normal vaginal flora. *FEMS Immunol Med Microbiol*, Vol. 32, No. 1, (December 2001), pp.37-41 ISSN 0928-8244

Ronald, A. (2003). The etiology of urinary tract infection: traditional and emerging pathogens. *Dis Mon*, Vol. 49, No. 2, (February 2003), pp. 71-82 ISSN 0011-5029

Ross, S. M. (2006). Clinical applications of cranberry in urinary tract infections. *Holist Nurs Pract*. Vol. 20, No. 4, (July-August 2006), pp.213-214 ISSN 0887-9311

Sack, R. B. & Froehlich, J. L. (1982). Berberine inhibits intestinal secretory response of *Vibrio cholerae* and *Escherichia coli* enterotoxins. *Infect Immun*, Vol. 35, No. 2, (February 1982), pp.471-475 ISSN 0019-9567

Scazzocchio, F., Cometa, M. F., Tomassini, L. & Palmery, M. (2001). Antibacterial activity of *Hydrastis canadensis* extract and its major isolated alkaloids. *Planta Med*, Vol. 67, No. 6, (August 2001), pp.561-564 ISSN 0032-0943

Schaeffer, A. J., Amundsen, S. K. & Jones, J. M. (1980). Effect of carbohydrates on adherence of *Escherichia coli* to human urinary tract epithelial cells. *Infect Immun*, Vol. 30, No. 2, (November 1980), pp.531-537 ISSN 0019-9567

Schaeffer, A. J., Chmiel, J. S., Duncan, J. L. & Falkowski, W. S. (1984). Mannose-sensitive adherence of *Escherichia coli* to epithelial cells from women with recurrent urinary tract infections. *J Urol*, Vol. 131, No. 5, (May 1984), pp.906-910 ISSN 0022-5347

Schaeffer, A. J. & Stuppy, B. A. (1999). Efficacy and safety of self-start therapy in women with recurrent urinary tract infection. *J. Urol.*, Vol. 161, No. 1, (January 1999), pp. 207-211 ISSN 0022-5347

Schindler, G., Patzak, U., Brinkhaus, B., von Niecieck, A., Wittig, J., Krähmer, N., Glöckl, I. & Veit, M. (2002). Urinary excretion and metabolism of arbutin after oral administration of *Arctostaphylos uva ursi* extract as film-coated tablets and aqueous solution in healthy humans. *J Clin Pharmacol*, Vol. 42, No. 8, (August 2002), pp.920-927 ISSN 1198-581X

Seeram, N. P. (2008). Berry fruits for cancer prevention: current status and future prospects. *J Agric Food Chem*, Vol. 56, No. 3, (February 2008), pp. 630-635 ISSN *0021-8561*

Siciliano, A. A. (1996). Cranberry. *HerbalGram,* Vol. 38, (September 1996), pp. 51-54 ISSN *0899-5648*

Sikkema, J., De Bont, J. A. M. & Poolman, B. (1994). Interactions of cyclic hydrocarbons with biological membranes. *J Biol Chem*, Vol. 269, pp. 8022-8028 ISSN 0021-9258

Simpson, D. (1998). Buchu – South Africa's amazing herbal remedy. *Scott Med J*, Vol. 43, No. 6, (December 1998), pp. 189-191 ISSN 0036-9330

Smith, R. D., Yago, M., Millar, M. & Coast, J. (2006). A macroeconomic approach to evaluating policies to contain antimicrobial resistance: A case study of methicillin-resistant *staphylococcus aureus* (MRSA). *Appl Health Econ Health Policy*, Vol. 5, No. 1, (January 2006), pp. 55-65 ISSN 1175-5652

Smith-Palmer, A., Stewartt, J &, Fyfe, L. (2002). Inhibition of listeriolysin O and phosphatidylcholine-specific production in *Listeria monocytogenes* by subinhibitory

concentrations of plant essential oils. *J Med Microbiol*, Vol. 51, No. 7, pp.567-574 ISSN 0022-2615

Smith-Palmer, A., Stewart, J. & Fyfe, L. (2004). Influence of subinhibitory concentrations of plant essential oils on the production of enterotoxins A and B and alpha-toxin by *Staphylococcus aureus*. *J Med Microbiol*, Vol. 53, No. 10, pp.1023-1027 ISSN 0022-2615

Spooner, J. B. (1984). Alkalinisation in the management of cystitis. *J Int Med Res*, Vol. 12, No.1 , (January 1984), pp.30-34 ISSN 0300-0605

Stamm, W. E., & Hooton, T. M. (1993). Management of urinary tract infections in adults. *N Engl J Med*, Vol. 329, No. 18, (October 1993), pp. 1328-1334 ISSN 0028-4793

Strassner, C. & Friesen, A. (1995). Therapy of candiduria by alkalinization of the urine. Oral treatment with potassium-sodium-hydrogen citrate. *Fortschr Med*, Vol. 113, No. 25, (September 1995), pp.359-362 ISSN 0015-8178

Sun, D., Abraham, S. N. & Beachey, E. H. (1988a). Influence of berberine sulfate on synthesis and expression of Pap fimbrial adhesin in uropathogenic *Escherichia coli*. *Antimicrob Agents Chemother*, Vol. 32, No. 8, (August 1988), pp.1274-1277 ISSN 1098-6596

Sun, D., Courtney, H. S. & Beachey, E. H. (1988b). Berberine sulfate blocks adherence of *Streptococcus pyogenes* to epithelial cells, fibronectin, and hexadecane. *Antimicrob Agents Chemother*, Vol. 32, No. 9, (September 1988), pp.1370-1374 ISSN 1098-6596

Tabibian, J. H., Gornbein, J., Heidari, A., Dien, S. L., Lau, V. H., Chahal, P., Churchill, B. M. & Haake, D. A. (2008). Uropathogens and host characteristics. *J Clin Microbiol*, Vol. 46, No. 12, (December 2008), pp. 3980-3986 ISSN 0095-1137

Türi, M., Türi, E., Kõljalg, S. & Mikelsaar, M. (1997). Influence of aqueous extracts of medicinal plants on surface hydrophobicity of *Escherichia coli* strains of different origin. *APMIS*, Vol. 105, No. 12, (December, 1997), pp.956-962 ISSN 1600-0463

Uva ursi. (2004). In: LaGow, B, chief editor. *PDR for Herbal Medicines*. 3rd ed. Montvale, NJ: Thomson; pp. 847-851 ISBN 1563635127

Vaughan, V. (2007). *C. difficile* endemic in health service. *Health Serv J*, Vol. 117, No. 6038, (January 2007), pp. 6 ISSN 0020-7314

Velraeds, M. M., van der Mei, H. C., Reid, G. & Busscher, H. J. (1996). Inhibition of initial adhesion of uropathogenic *Enterococcus faecalis* by biosurfactants from Lactobacillus isolates. *Appl Environ Microbiol*, Vol. 62, No. 6, (June 1996), pp.1958-1963 ISSN 0099-2240

Weiss, E. L., Lev-Dor, R., Sharon, N. & Ofek, I. *(2002).* Inhibitory effect of a high-molecular-weight constituent of cranberry on adhesion of oral bacteria. *Crit Rev Food Sci Nutr*, Vol. 42, No. 3, pp.285-292 ISSN 1040-8398

Wellens, A., Garofalo, C., Nguyen, A. M., Van Gerven, N., Slättegård, R., Hernalsteens, J. P., Wyns, L., Oscarson, S., De Greve, H., Hultgren, S. & Bouckaert, J. (2008). Intervening with urinary tract infections using anti-adhesives based on the crystal structure of the FimH-oligomannose-3 complex. *PLoS One*, Vol. 3, No. 4, (April 2008), pp.e2040 ISSN *1932-6203*

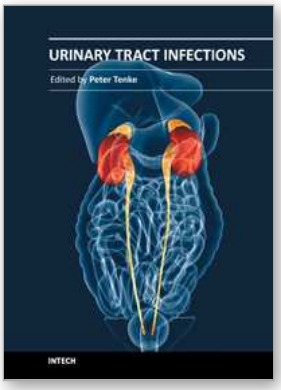
Wendakoon, C. N. & Sakaguchi, M. (1995). Inhibition of amino acid decarboxylase activity of *Enterobacter aerogenes* by active components in spices. *J Food Prot*, Vol. 58, pp.280-283 ISSN 0362-028X

Wieser, A., Romann, E., Magistro, G., Hoffmann, C., Nörenberg, D., Weinert, K. & Schubert, S. (2010). A multiepitope subunit vaccine conveys protection against extraintestinal pathogenic *Escherichia coli* in mice. *Infect Immun*, Vol. 78, No. 8, (August 2010), pp.3432-3442 ISSN 0019-9567

Wollenweber, E. (1988). Occurrence of flavonoid aglycones in medicinal plants. *Prog Clin Biol Res*, Vol. 280, pp. 45-55 ISSN 0361-7742

Yan, D., Jin, C., Xiao, X. H. & Dong, X. P. (2008). Antimicrobial properties of berberines alkaloids in Coptis chinensis Franch by microcalorimetry. *J Biochem Biophys Methods*, Vol. 70, No. 6, (April 2008), pp.845-849 ISSN 0165-022X

Yilmaz, A., Bahat, E., Yilmaz, G. G., Hasanoglu, A., Akman, S. & Guven, A. G. (2007). Adjuvant effect of vitamin A on recurrent lower urinary tract infections. *Pediatr Int*, Vol. 49, No. 3, (June 2007), pp.310-313 ISSN 1442-200X



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Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, and they are also the leading cause of hospital-acquired infections. Therefore, the appropriate management of UTIs is a major medical and financial issue. This book covers different clinical manifestations of UTI, with special emphasis on some hard-to-treat diseases, and special conditions in respect of treatment; antibiotic resistance and the available alternative strategies for the prevention and treatment of UTIs and it deals with urinary tract infections in children. The aim of this book is to give a summary about the different aspects of the diagnosis, management and prevention of urinary tract infections for all medical disciplines.

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