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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 proctitis 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, frequently 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 trimethoprim-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 berberine 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 faecalis* 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 lactobacilli 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. rhamnosus* 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 identified 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

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