

Microbial Protection: How Probiotics Guard Against UTIs?

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Abstract

The increasing prevalence of bacteria that resist antibiotics has had a significant influence on the way we treat urinary tract infections (UTIs). This problem has increased treatment costs and put additional strain on healthcare systems. As a result, experts are looking at different therapy options, especially for women who have recurring UTIs. Probiotic supplements, particularly those featuring *Bifidobacterium* and *Lactobacillus* strains, could serve as an effective preventive measure. Recent study contradicts the traditional notion that the urine system is sterile, demonstrating the presence of a resident microbiome, which plays a critical role in sustaining urinary health. According to various literature reviews, probiotics can prevent and treat urogenital infections effectively. According to this research, probiotics may be a good first-line treatment for changing the urine microbiota, which might have preventative and therapeutic effects on numerous urinary illnesses.

Healthcare professionals, researchers, and policy makers must accurately assess essential aspects, such as the best bacterial strains, viable cell counts, and appropriate administration routes. To fully utilize the benefits of probiotic therapy, we need to standardize key components. This ensures that we achieve consistent and reliable results for different groups of patients. We aim to improve patient health while alleviating the rising healthcare challenges associated with UTIs.

As antibiotic resistance becomes a more pressing, our commitment to developing and rigorously assessing scientifically backed alternatives, including probiotic treatments, is more critical than ever.

1. Introduction

Urinary tract infections (UTIs) are common bacterial infections that occur when bacteria enter the urethra and ascend into the urinary system, prompting an inflammatory immune response. These infections primarily affect women and older men. It's important to note that unlike bacteriuria, which may not show symptoms, a UTI is marked by noticeable symptoms associated with inflammation (1, 2). The clinical definition of a urinary tract infection (UTI) involves a positive urine culture alongside specific symptoms (3). These infections typically manifest as painful uri-

nation, an increased need to urinate, urgency, blood in the urine, and sometimes even incontinence. While some people may experience a UTI just once, which usually resolves on its own or can be treated with antibiotics, others may be more susceptible to recurring infections and face repeated episodes (4). Studies suggest that between 50% and 60% of women will encounter a urinary tract infection (UTI) at some point in their lives, with around 20% to 30% likely to face recurrent infections later on (5-7). Recurrent infections can lead to significant health issues and place a heavy financial strain on individuals due to the high annual costs associated with diagnosis

and treatment. It's crucial to address urinary tract infections (UTIs) promptly, as untreated cases can result in serious complications like kidney infections or sepsis. Factors that increase the risk of UTIs include urinary tract blockages and urine retention, which may occur in conditions such as benign prostatic hyperplasia, urinary strictures, constipation, and neurogenic bladder (8). Patients who have certain conditions face an increased risk of recurrent or persistent infections. Moreover, individuals with comorbidities such as high blood sugar, low estrogen levels, pregnancy, kidney stones, chronic or intermittent catheter use, anatomical abnormalities, or the presence of foreign bodies are particularly susceptible to bacterial invasion of the urothelium (9). The primary reason for urinary tract infections (UTIs) in premenopausal women is the movement of pathogens, particularly uropathogenic *Escherichia coli*, from the rectum or vagina to the urethra during sexual intercourse. To help prevent UTIs, it's important to adopt certain behaviors such as staying well-hydrated, wiping from front to back, ensuring regular bowel movements, and urinating after sexual activity (10).

It is advisable for premenopausal women to receive a single-dose antibiotic after sexual activity if they experience related symptoms. When symptoms arise, patients are often prompted to submit urine samples for culture, which helps physicians create accurate antibiograms. This is crucial, as antibiotics play a key role in managing urinary tract infections (UTIs). Typically, antibiotics result in complete remission of the disease. However, for those facing recurrent urinary tract infections (rUTIs), which the American Urology Association defines as having two or more UTIs within six months or three or more in a year, patients might need several prescriptions or longer courses of antibiotics for effective treatment. For individuals with rUTIs, the current approach to prevention involves a long-term, low-dose regimen of antimicrobial agents like trimethoprim or nitrofurantoin (11). Some bacteria have developed resistance to commonly prescribed antibiotics, which can lead to recurrent UTIs due to the inability to effectively eliminate these bacteria. This challenge has spurred research into alternative non-antibiotic treatments, including methenamine-hippurate, cranberry tablets, D-mannose, and probiotics. These options are believed to help mitigate microbial resistance by decreasing reliance on anti-

biotic therapies (12). The exploration of probiotics in managing recurrent urinary tract infections (rUTIs) is a promising and evolving area of research. Recent studies have challenged the traditional belief that the human bladder is completely sterile, highlighting the presence of a distinct genitourinary microbiome (13, 14). Research has shown that, much like the gastrointestinal tract, the urogenital tract is home to a diverse range of microbes. These microorganisms contribute to maintaining a balanced urinary environment by influencing local metabolite levels and pH (14).

Research has uncovered intriguing differences in the balance of microorganisms between healthy individuals and those plagued by frequent urinary tract infections (UTIs). Notably, *Lactobacillus iners*, *Lactobacillus crispatus*, and *Lactobacillus jensenii* stand out as the dominant forces in nurturing a balanced urinary microbiome (15-17). Intravaginal estrogen, a thoroughly researched and proven method of non-antibiotic prevention for urinary tract infections in postmenopausal women, has been demonstrated to enhance the levels of *Lactobacillus* in the vagina, contributing to better vaginal health (18). The proposed mechanism operates by creating a more acidic environment within the vaginal canal. Lactic acid-producing bacteria, known as LB, play a crucial role in this process, leading to a noticeable drop in vaginal pH. This lower pH acts as a barrier against harmful microorganisms, offering a protective shield that significantly reduces the chances of recurrent urinary tract infections (19). Research suggests that supplementing with probiotics, or beneficial microorganisms, may help establish protective microbial populations in the urinary tract, aiding in the prevention of urinary tract infections (UTIs) and promoting overall urinary health. As a result, probiotics are being considered as a non-medicated option for UTI prevention (20, 21).

2. Urinary Tract Infections (UTIs)

Urinary Tract Infections (UTIs) are among the most frequent bacterial infections, affecting millions of individuals annually. The bladder (cystitis) and urethra (urethritis), though they can progress to the upper tract, such as the kidneys

(pyelonephritis), if untreated. Women are significantly more prone to UTIs due to their shorter urethras and anatomical proximity of the urethral opening to the rectum. Common symptoms include a strong, persistent urge to urinate, a burning sensation during urination, cloudy or strong-smelling urine, and pelvic pain. In severe cases, fever and flank pain may indicate kidney involvement. Early diagnosis and treatment are crucial to prevent complications, with antibiotics being the most common therapeutic option (22). Preventive measures against UTIs include staying hydrated, practicing good personal hygiene, and urinating after sexual activity to minimize bacterial transfer. Additionally, avoiding the use of irritating feminine products and adopting a diet rich in probiotics can contribute to a healthy urinary tract. Recurrent UTIs, particularly in women, often necessitate further medical evaluation to identify underlying causes like anatomical abnormalities or resistant bacterial strains. Advances in medical research are exploring alternative treatments, such as immunotherapy, and the development of vaccines to reduce recurrence rates. Understanding the risk factors, timely intervention, and adherence to prescribed treatments are fundamental for managing UTIs effectively and improving the quality of life for affected individuals (23).

2.1 Pathogenesis: How do bacteria cause UTIs?

Urinary tract infections (UTIs) are predominantly caused by bacteria that ascend from the urethra to the bladder and, in severe cases, to the kidneys. *Escherichia coli* is the most common pathogen responsible. Upon entering the urinary tract, *E. coli* utilizes specialized adhesive structures called pili or fimbriae to attach to the epithelial cells lining the urinary tract. This adhesion prevents the bacteria from being washed away during urination, allowing them to colonize and proliferate effectively (24). After successful colonization, bacteria such as *E. coli* initiate an inflammatory response in the host's urinary tract. By releasing toxins and enzymes, these bacteria damage epithelial cells, further facilitating their invasion. One key component of this damage is the disruption of cell membranes, leading to cell death and the release of nutrients

that promote further bacterial growth. This inflammatory response is often characterized by symptoms such as burning during urination, frequency, and urgency. Host immune factors play a crucial role in controlling bacterial infections in the urinary tract. Neutrophils are rapidly recruited to the site of infection to phagocytize bacteria and release antimicrobial factors. However, virulent strains of bacteria have developed mechanisms to evade immune detection, such as the formation of biofilms. Biofilms provide a protective matrix that shields bacteria from both immune responses and antibiotics, leading to persistent and recurrent infections (25).

2.2 Common causative agents UTIs

Urinary Tract Infections (UTIs) are among the most common bacterial infections globally, impacting millions each year. One of the principal causative agents of UTIs is *Escherichia coli*, which accounts for approximately 70–90% of community-acquired infections. This pathogen resides in the gastrointestinal tract and can easily colonize the urinary tract, particularly in females due to their shorter urethras. Other germs like *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Staphylococcus saprophyticus* are also significant contributors to the pathology of UTIs. These agents are mostly opportunistic pathogens that exploit breaches in host defense mechanisms, leading to infection (26). The virulence of UTI-causing pathogens is often attributed to their unique ability to adhere to the epithelial lining of the urinary tract using specialized fimbriae or pili. For instance, *E. coli* possesses P-fimbriae and Type 1 fimbriae, which facilitate attachment to uroepithelial cells and resist urinary flow. contributes to chronic or recurrent infections by protecting pathogens from antibiotics and immune responses. Other pathogens, such as *Proteus mirabilis*, not only adhere but also hydrolyze urea, creating alkaline conditions that facilitate stone formation and chronic urinary complications (24). The management and prevention of UTIs rely on understanding the specific characteristics of these pathogens. Antibiotic therapy is often tailored based on the predominant causative agent in a region, with *E. coli* being the primary target.

However, the emergence of multidrug-resistant (MDR) strains presents a growing challenge in UTI management, necessitating advanced diagnostic tools and personalized treatment approaches. Preventive strategies, including stringent hygiene, adequate hydration, and addressing risk factors such as catheter usage, are pivotal in curbing infections. Moreover, vaccine development targeting virulence factors like fimbriae and biofilms offers promising potential for reducing UTI incidence (27).

2.3 Symptoms and complications of recurrent UTIs

Recurrent urinary tract infections (UTIs) often manifest with a variety of symptoms which may vary in intensity and frequency. The most common symptoms include a strong, persistent urge to urinate, a burning sensation during urination, and passing frequent, small amounts of urine. Other signs might involve cloudy or strong-smelling urine, pelvic pain (especially in women), low-grade fever, and sometimes blood in the urine. These symptoms can significantly disrupt daily life, especially when they occur frequently or go untreated (28). If recurrent UTIs are not properly managed, they can lead to several severe complications. One prominent risk is kidney infection (pyelonephritis), which can develop when bacteria travel up to infect the kidneys. This can result in high fever, back pain, nausea, and vomiting, and in extreme cases, it may cause permanent kidney damage. Recurrent UTIs may also weaken the bladder, leading to bladder dysfunctions and reduced quality of life. Furthermore, systemic infections like sepsis can occur if the bacteria enter the bloodstream, which can be life-threatening. Preventive strategies and prompt treatment play a crucial role in reducing the risk and impact of recurrent UTIs. Drinking plenty of water, maintaining proper hygiene, urinating after sexual activity, and avoiding potential irritants such as certain feminine products can help prevent these infections. Patients with recurrent UTIs might also benefit from low-dose preventive antibiotics or other medical interventions guided by a healthcare professional. Early diagnosis and treatment are essential to prevent

complications and ensure the condition does not progress to more severe stages (29).

3. Probiotics as Natural Defenders Against UTIs

Probiotics are known as natural defenders against urinary tract infections (UTIs). Numerous studies have shown that probiotics can play an important role in the prevention and treatment of UTIs by interfering with the growth and proliferation of pathogenic bacteria in the urinary tract (30). Research has shown that probiotic use, especially in people prone to recurrent urinary tract infections, can reduce the incidence of these types of infections. In general, probiotics are considered a low-risk and effective treatment option in UTIs management (30, 31).

3.1 Definition of probiotics and their role in maintaining microbial balance

Probiotics are living microorganisms that, when consumed in the right quantities, have beneficial effects on the health of the host, including microorganisms such as bacteria and yeasts that are naturally present in the human body or can enter the body as dietary supplements (32). Probiotics are usually extracted from *Lactobacillus* and *Bifidobacterium* bacteria, especially in fermented dairy products (33). The beneficial effects of probiotics are mainly related to maintaining the balance of the intestinal microbiota and strengthening the immune system (34). Gut microbiota plays a key role in human health, and imbalances can lead to various diseases and disorders. Probiotics prevent digestive problems, intestinal inflammation, and even immune system disorders by balancing beneficial and harmful microorganisms in the intestines (35). Probiotics are able to help reduce intestinal inflammation and have positive effects in treating intestinal disorders such as irritable bowel syndrome and ulcerative colitis (36). Taking probiotics can also help boost the immune system and prevent infections. In fact, probiotics can improve the immune response by stimulating the production of antibodies and affecting the activity of immune cells such as macrophages and lymphocytes. These mechanisms can help prevent infectious diseases and even some cancers (37).

3.2 Mechanisms of action of Probiotics

The effects of probiotics are particularly pronounced in the digestive tract and immune system, and they can help restore microbial balance in the gut and promote general health through various mechanisms (38). Mechanisms such as competition for food sources and biospace, the production of antibacterial substances, strengthening the intestinal barrier, modulating the immune response, effects on the metabolism and function of the intestinal microbiota, reducing inflammation and antiallergic effects help maintain the health of the body. These mechanisms indicate the complexity and extent of the effects of probiotics on human health (39, 40).

3.2.1 Competitive exclusion of pathogenic bacteria

Probiotics are known as natural defenses against urinary tract infections (UTIs) (41). These living microorganisms can prevent the growth of pathogenic bacteria by creating competition for nutritional and spatial resources (32). One of the main mechanisms of this effect is competitive exclusion, in which probiotics effectively compete with pathogens to adhere to epithelial cells and absorb nutrients (42). Research has shown that probiotics can reduce the growth of infectious bacteria such as *E. Coli* and *Klebsiella* in the urinary tract, reduce the risk of UTIs (30). In addition, probiotics can make the environment unfavorable for the growth of pathogenic bacteria by producing lactic acid and other antibacterial compounds. Overall, the use of probiotics as a strategy to prevent urinary tract infections in susceptible people is becoming a promising approach (37).

3.2.2 Production of antimicrobial substances

Probiotics are able to make the environment unfavorable for the growth of pathogenic bacteria by producing compounds such as lactic acid, hydrogen peroxide, and bacteria (43). Probiotics can use these methods to prevent the growth of pathogens such as (*E. Coli*) which is the main cause of UTIs, are prevented. In addition to suppressing the growth of pathogens, these antibacterial compounds help strengthen the normal flora of the uri-

nary tract and prevent the overgrowth of pathogenic microorganisms (44). Also, some probiotics can reduce the risk of urinary infections by inhibiting the production of toxins by pathogenic bacteria. As a result, the use of probiotics as a natural strategy for the prevention and treatment of UTIs through the production of antibacterial substances is a promising approach in medicine (30).

3.2.3 Strengthening the epithelial barrier

The epithelial dam plays an important role in protecting the body from pathogens, and probiotics can strengthen this dam through several mechanisms (45). First, probiotics can create an unfavorable environment for pathogenic bacteria to grow by producing antibacterial compounds such as lactic acid and hydrogen peroxide, thereby helping to reduce the adhesion of pathogens to epithelial cells (43). Also, probiotics are able to modulate the production of inflammatory cytokines and prevent unnecessary inflammation in epithelial tissues, which leads to the maintenance of the integrity of the epithelial dam (46). Some studies have shown that probiotics can reduce epithelial permeability by improving the activity of intercellular binding proteins, such as claudines and eucloclines, and prevent pathogens from entering epithelial cells. In addition, probiotics can strengthen the normal flora, which itself helps maintain the epithelial barrier and prevents the growth of harmful bacteria (47). These characteristics present probiotics as a potential tool for the prevention and treatment of UTIs, especially in people prone to recurrent urinary tract infections. As a result, the strengthening of the epithelial dam by probiotics can be considered as one of the important mechanisms in the Prevention of UTIs (46, 47).

3.2.4 Modulation of the immune system

Probiotics play an important role as a natural defense against urinary tract infections (UTIs) through immune modulation. Probiotics can prevent UTIs by altering immune function and regulate immune responses in a way that effectively prevents urinary tract infections (48). Probiotics, especially by stimulating the production of certain cytokines and antibodies in response to pathogens, can strengthen the immune response (49).

These microorganisms can also increase the activity of immune cells such as macrophages and dendritic cells, thereby strengthening the immune response at the site of infection. In addition, probiotics can prevent urinary tract infections by stimulating the Th1 and Th17 responses, which are responsible for defending against pathogenic bacteria (50). In addition, probiotics can inhibit inflammation by reducing the production of inflammatory cytokines such as IL-6 and TNF- α , thus preventing tissue damage from chronic infections (43). As a result, the modulating effects of probiotics on the immune system can be considered an effective strategy for the prevention and treatment of UTIs, especially in people prone to recurrent infections (48).

4. Key Probiotic Strains for UTI Prevention and Treatment

Urinary tract infections (UTIs) are a significant health concern, characterized by the colonization of pathogen bacteria such as *Escherichia coli* in the urinary tract. Probiotics, which are live beneficial microorganisms, have emerged as a potential preventive and therapeutic approach to UTIs. Specific strains like *Lactobacillus crispatus* and *Lactobacillus rhamnosus* are particularly effective. These strains produce lactic acid, which lowers the pH of the urinary tract, creating an environment hostile to pathogens. Additionally, they adhere to epithelial surfaces, forming a protective barrier against bacterial adhesion. Research suggests that including strains such as *Lactobacillus reuteri* and *Lactobacillus casei* in the diet can further enhance urinary health. These probiotics modulate the immune response, reducing inflammation caused by infections. They also suppress the growth of uropathogens by competing for adhesion sites and resources. Clinical trials have shown that regular probiotic supplementation can significantly decrease UTI recurrence, offering a natural and antibiotic-free solution for long-term management. An emerging area of study highlights the role of multi-species probiotic formulations in UTI prevention. Instead of relying on single strains, these formulations combine several probiotic strains like *Bifidobacterium bifidum* and *Saccharomyces bou-*

lardii, which work synergistically to enhance urinary tract health. This approach targets different aspects of pathogen resistance, including immune modulation, biofilm disruption, and prevention of bacterial colonization. As UTIs are becoming increasingly resistant to antibiotics, probiotics offer a sustainable and holistic alternative for both prevention and treatment (26, 51, 52).

5. Probiotic Delivery Systems

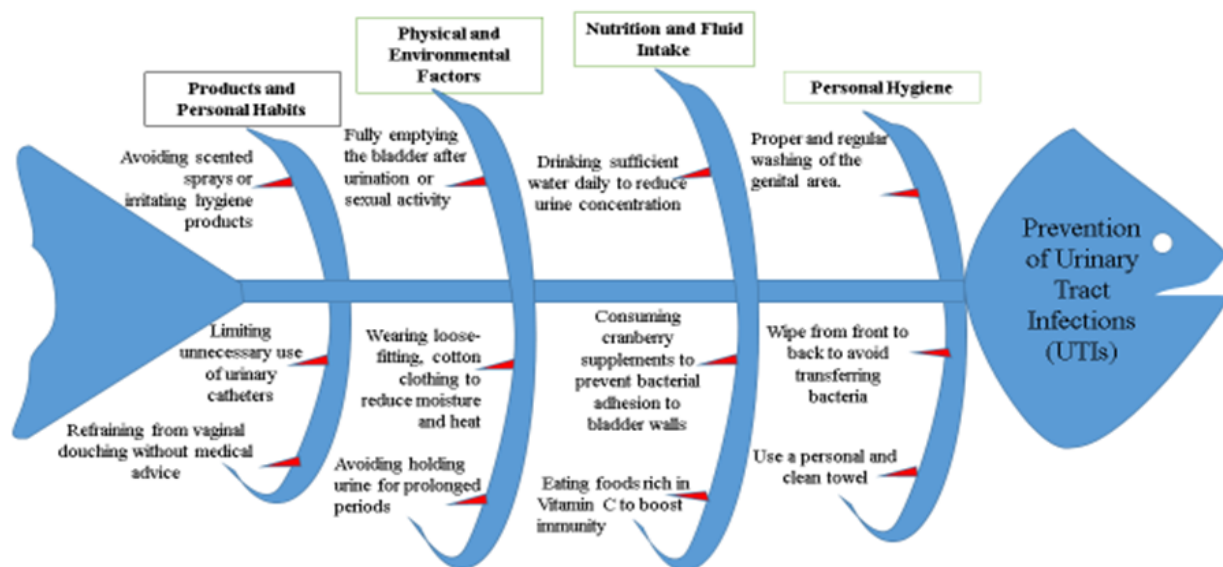
Probiotic delivery systems play a crucial role in ensuring that the beneficial microorganisms reach the target site in the body, where they can exert their health benefits. Different delivery methods are available, each with its own advantages and limitations (53). The selection of the most appropriate delivery system depends on factors such as the type of infection, the targeted region of the body, and the characteristics of the probiotic strain being used. In the context of urinary tract infections (UTIs), the main delivery systems include oral supplements, vaginal probiotics, and a variety of methods to deliver probiotics directly to the urinary tract. Understanding the effectiveness of each delivery system is essential to determine which is most beneficial for UTI prevention and treatment (25). Formulation and delivery methods can significantly impact the safety and efficacy of probiotics. Various formats, including capsules, tablets, and powders, can differently influence the survival, viability, release, and colonization of probiotic strains in the urinary tract. Therefore, selecting the appropriate formulation and delivery method is crucial to ensuring both their safety and effectiveness (53). The optimal drug for treating urinary tract infections (UTIs) is defined by its ability to be absorbed into specific target tissues, maintain therapeutic concentrations at the intended site of action, and exhibit minimal systemic toxicity. The pharmacological management of UTIs poses several distinct challenges in meeting these goals. Firstly, the structural characteristics of the urothelial lining, which provide a protective barrier against the harsh environment of the urinary tract, can also hinder the penetration of drugs. The human uroepithelium establishes a bladder permeability barrier (BPB) that is similar to the blood-brain barrier.

Table1. Common causes of UTIs

Microorganism	Description	Sources
Escherichia coli	The most common cause of UTIs, especially in lower urinary tract infections.	(22-24, 26)
Proteus	Can alkalize urine by producing urease, facilitating kidney stone formation.	(24)
Klebsiella	Commonly observed in nosocomial infections.	(26)
Enterococcus	A common cause of UTIs in hospitalized patients using urinary catheters.	(26)
Staphylococcus saprophyticus	More commonly seen in young sexually active women.	(26)

Table 2. Frequent UTIs

Frequent UTIs Factor	Description	Sources
Biological Susceptibility	Due to urinary tract structure or genetic factors.	(22-29, 51, 52)
Risky Behaviors	Such as frequent catheter use, prolonged holding of urine, or insufficient water consumption.	(22-29, 51, 52)
Bacterial Persistence	Bacteria may remain even after treatment.	(22-29, 51, 52)
Improper Antibiotic Use	Leads to drug resistance.	(22-29, 51, 52)
Underlying Conditions	Diseases like diabetes or urinary tract abnormalities.	(22-29, 51, 52)



This BPB is reinforced by tight junctions, a dense arrangement of rigid plaques made up of uroplakins, and a hydrophilic mucin layer on the luminal surface that obstructs drug molecules from accessing the underlying cell membranes (54). Furthermore, the bioavailability of drugs administered through the intravehicular route is reduced due to dilution and washout effects resulting from urinary flow. Consequently, it is often necessary to administer higher doses of antibiotics to achieve therapeutic levels in the targeted tissues, which in turn raises the risk of adverse effects. Additionally, inadequate dosing can lead to the development of antibiotic resistance (55).

5.1 Oral supplements: Capsules, powders, and beverages

Oral probiotic supplements, available in the form of capsules, powders, and beverages, are the most commonly used delivery methods. These supplements typically contain freeze-dried or active strains of beneficial bacteria such as *Lactobacillus* or *Bifidobacterium*, which are selected for their ability to survive passage through the digestive system and colonize the urinary tract. Capsules and powders offer convenience, as they can be taken with water, while beverages are often marketed as more enjoyable, especially for those who have difficulty swallowing pills. Once ingested, probiotics pass through the gastrointestinal tract, where they can either exert their effects locally or be absorbed and distributed throughout the body. In the case of UTIs, the probiotics from oral supplements are thought to reach the urinary tract through the bloodstream, where they can help restore the microbial balance and reduce the risk of infection (56). The concept of administering oral probiotics is founded on the understanding that the pathogens responsible for the majority of urogenital infections migrate from the rectal area to the perineal region, subsequently reaching the vagina and mesentery. If harmful bacteria are capable of this progression, it raises the question of why *Lactobacillus*, a crucial element in vaginal colonization, cannot follow suit. Clinical research has shown that the oral intake of *Lactobacillus* can yield beneficial effects once it arrives in the vagi-

nal environment (30). However, the effectiveness of oral probiotics for UTI prevention can be variable, as the microorganisms must survive the acidic environment of the stomach and reach sufficient concentrations in the urinary tract to have a therapeutic effect. Studies have shown that *Lactobacillus* species can remain viable in the intestines and subsequently colonize the urinary tract, though the levels needed for clinical efficacy remain under investigation (30). Probiotics may serve as a viable alternative to antibiotic treatment due to their capacity to adhere to uroepithelial cells, thereby hindering the growth of pathogens and promoting the secretion of biosurfactants. Oral administration of *Lactobacillus* can lead to the colonization of these bacteria within the urinary tract after they have established themselves in the intestines (57). Probiotic capsules comprising *lactobacillus. rhamnosus* and *lactobacillus. fermentes* were taken orally at a dosage of 10^9 CFU either once or twice each day. The oral administration of these probiotic capsules could potentially modulate the vaginal microbiota and may prove beneficial in managing recurrent urinary tract infections (UTIs). Furthermore, it was highlighted that oral probiotics might offer greater comfort to patients compared to vaginal delivery methods, which could enhance adherence to the treatment regimen (58-60). The efficacy of orally administered probiotics in decreasing the recurrence of urinary tract infections (UTIs) has been evaluated. Study on *Bifidobacterium. longum*, demonstrating a 70% reduction in lower UTIs caused by Candida infections among women who received oral *Bifidobacteriu. longum* (61). Several in vitro and in vivo studies support the beneficial effect of some strains of *lactobacillus* on the restoration of the vaginal flora and the prevention of recurrent UTIs. Most of them show that *lactobacillus. rhamnosus* GR-1 and *lactobacillus. Fermentum* genital RC-14, given either intravaginally or orally, are efficacious (62).

5.2 Vaginal probiotics: Suppositories and creams

Vaginal probiotics offer a targeted delivery method for individuals who are looking to directly influence the vaginal and urinary microbiota.

Since the urinary tract and vaginal microbiota are closely related, particularly in women, maintaining a healthy vaginal microbiome is critical for UTI prevention. Vaginal probiotics are typically delivered through suppositories or creams that contain live bacterial strains, often *Lactobacillus* species. These probiotics are inserted into the vagina, where they can more directly influence the microbial environment, particularly by increasing the population of beneficial *Lactobacillus* species and decreasing the presence of harmful pathogens such as *E. coli*. Vaginal delivery systems allow for a higher concentration of probiotics to reach the target area, which may enhance their efficacy in preventing infections. Studies suggest that vaginal probiotics can help restore the natural pH and balance of the vaginal microbiota, preventing the overgrowth of pathogenic bacteria (63, 64). Additionally, vaginal probiotics may be more effective for individuals with recurrent UTIs, as they allow for the delivery of probiotics directly to the site of infection. However, challenges with this delivery method include potential user discomfort, difficulty in consistent application, and the need for frequent use to maintain therapeutic effects. A well-defined and established connection exists between vaginal flora and urogenital infections. The majority of microorganisms found in the vagina originate from the gastrointestinal tract, in addition to factors related to personal hygiene. In a healthy vaginal environment, *Lactobacillus* spp. predominates. Numerous scientific studies have indicated that the management of gastrointestinal and vaginal flora through probiotic supplementation may help in the prevention of genitourinary infections (64). The correction of vaginal microflora necessitates the inclusion of *Lactobacillus* species in probiotics designed to prevent and treat genitourinary infections. Probiotics may function through various mechanisms, including the inhibition of pathogen adhesion, the acidification of the mucosal surface, the enhancement of the host's immune response through synergistic interactions and the production of beneficial substances such as vitamins and immunomodulators (65). Certain species of *Lactobacillus* are known to generate hydrogen peroxide and biosurfactants, which contribute to

the acidification of the vaginal mucosa. The efficacy of these characteristics, along with their biomimetic regulatory effects, has been substantiated. These attributes render *Lactobacillus* the probiotic of choice for both the prevention and treatment of urogynecologic infections (66). Vaginal administration of *Lactobacillus* probiotics is both safe and effective in preventing recurrent urinary tract infections (UTIs) in adult women. The findings indicated that ovules containing combinations of *L. crispatus* CTV05 or *L. rhamnosus* GR-1 along with *L. fermentum* B-54 were the most effective approaches. The analysis also underscored the need for an increased number of randomized clinical trials to evaluate the effectiveness of oral probiotic therapies (67). In recently clinical trial supplementation with 480 mg *L. rhamnosus* GR-1 and *L. reuteri* RC-14 significantly though incompletely decreased the mean number of recurrences in patients with uncomplicated UTI relative to the control. In addition, antibiotic resistance was significantly reduced in the probiotic group compared to the control group (68). In a study showed that vaginal suppositories with *Lactobacillus. crispatus* GAI 98332 could decrease the recurrence of UTI significantly without any adverse complication during treatment (69). *Lactobacillus. crispatus* can be easily isolated from the vaginas of healthy women and is almost capable of producing hydrogen peroxide as well as adhering to vaginal epithelial cells (70). The study indicates that the hydrogen peroxide production of three *Lactobacillus. crispatus* strains was evaluated, leading to the selection of strain GAI 98332, which exhibited the highest hydrogen peroxide production levels (71). A study of 42 subjects was undertaken whereby vaginal suppositories were administered following treatment of UTI with different antibiotics (72). In this case, the occurrence of urinary tract infections was diminished among patients who received treatment with trimethoprim–sulfamethoxazole and subsequently underwent intravaginal instillation of probiotic lactobacilli. Vaginal immunization is another noteworthy UTI treatment approach to confer mucosal immunity, thereby reducing susceptibility to common uropathogens. A double-blind phase II clinical trial in 75 patients evaluated the efficacy

of vaginal suppositories containing either multiple strains of heat-killed uropathogenic bacteria or placebo (73). Women receiving the vaccine experienced a markedly reduced incidence of *E. coli* urinary tract infections in comparison to those in the placebo group. Additionally, the vaccine group exhibited a lower overall infection rate from various bacteria, although this finding did not reach statistical significance. Furthermore, a phase II clinical trial was conducted to assess the impact of *Lactobacillus. crispatus* probiotic suppositories (Lactin-V) on the recurrence of urinary tract infections (20). Vaginal suppositories containing lactobacilli present a promising area of investigation, as the preservation of normal vaginal flora, predominantly consisting of lactobacilli, is linked to lower incidences of urinary tract infection (UTI) recurrence (74). *Lactobacillus* suppositories aim to restore normal vaginal flora and exert a protective effect against UTIs by main mechanisms of the discharge of antimicrobial agents, including lactic acid, out-competing pathogenic bacteria, preventing the adhesion of pathogens to epithelial cells, non-specific stimulation of the innate immune system. *Lactobacillus* suppositories not only help in preventing bacterial resistance but also mitigate the adverse effects associated with prolonged antibiotic use, including yeast vaginitis (75). The protective layer established by *Lactobacillus* against uropathogens inherently diminishes the likelihood of urinary tract infections (UTIs) and distinguishes *Lactobacillus* suppositories from conventional prophylactic antibiotics. Intravaginal suppositories that incorporate *Lactobacillus crispatus* CTV05, *Lactobacillus rhamnosus* GR1, and *Lactobacillus reuteri* RC14 demonstrate notable effectiveness against uropathogens and exhibit superior efficacy in the prevention of urinary tract infections (UTIs). Importantly, these probiotic suppositories are generally well-tolerated, presenting no significant adverse effects, and they address the increasing concern of antibiotic resistance. Probiotic suppositories are thought to exert their prophylactic effects through bacteriostatic and bactericidal means. Consequently, the clinical and public health advantages of utilizing *Lactobacillus* suppositories are considerable when compared to the prolonged use of antibiotics (25).

5.3 Comparison of delivery methods in terms of effectiveness

Numerous innovative methods and technologies present promising solutions to address traditional challenges. Delivery systems designed to exhibit synergistic antimicrobial properties, precise targeting, and improved bioavailability enhance therapeutic efficacy and lead to better patient outcomes. Many of these delivery approaches demonstrate clinical applicability in urology, particularly in the management of urinary tract infections (UTIs), providing benefits over standard treatment methods (55). When comparing the effectiveness of oral and vaginal probiotic delivery methods, it is important to consider factors such as convenience, comfort, and therapeutic outcomes. Oral probiotics are easy to take and are generally more convenient, but they face significant challenges in terms of survival through the digestive system and their ability to reach high concentrations in the urinary tract. Studies have shown mixed results, with some indicating that oral probiotics can reduce the incidence of UTIs, while others suggest limited benefits (30). In contrast, vaginal probiotics are more effective for direct application to the target area, bypassing the digestive system entirely. This targeted approach has been shown to provide higher concentrations of probiotics to the vaginal and urinary microbiota, resulting in more immediate and noticeable benefits. Several studies have reported that vaginal probiotics can be particularly effective for individuals with recurrent UTIs, as they help restore the natural microbial balance in the vagina (53). While both methods have demonstrated efficacy, vaginal probiotics are often seen as more effective for localized infections due to their direct delivery to the site of need. A study indicated that *Lactobacillus. rhamnosus* GR-1 and *Lactobacillus. fermentum* RC-14 can effectively reach the vaginal environment when administered orally. Their intake led to notable alterations in the vaginal microbiota, particularly an increase in the presence of lactobacilli, specifically within the vancomycin-insensitive segment of the bacterial community, which includes the species *Lactobacillus. rhamnosus* and *Lactobacillus. fermentum*.

Although the study was not structured to explore mechanisms, the findings suggest that the oral administration of these strains facilitated the colonization of the vaginal microflora. A high concentration in fecal samples does not necessarily equate to a high concentration in vaginal swabs. Furthermore, vaginal colonization appears to predominantly occur during the second week of administration. Notably, *Lactobacillus. rhamnosus* GR-1 demonstrates greater efficacy in both intestinal and vaginal colonization compared to *Lactobacillus. fermentum* RC-14, which shows slightly reduced efficiency (60).

6. clinical trials demonstrating the benefits of probiotics for UTI prevention

Several clinical studies have shown that probiotics can be effective in preventing urinary tract infections (UTIs). These studies show that the use of probiotics, especially in women with a history of recurrent urinary infections, can reduce the incidence of UTIs (76). For example, a study found that daily consumption of probiotics including *Lactobacillus* for 12 weeks significantly reduced the number of urinary infections in healthy women (77). Also, another study found that probiotics can reduce the growth of pathogenic bacteria such as (*E. Coli*) in the urinary tract, reduce the risk of UTIs in susceptible people (77). In another research, showed that the use of probiotics *Lactobacillus* increases the production of lactic acid and hydrogen peroxide in the urine, which inhibits the growth of pathogenic bacteria. In addition, the results of a systematic clinical trial in 2019 showed that the use of probiotics in older women can effectively reduce the risk of urinary infections (37). This clinical evidence increasingly suggests that probiotics can be used as a noninvasive and natural method of UTIs prevention.

7. Benefits of Probiotics Over Antibiotics

Probiotics are gaining attention as a promising alternative to traditional antibiotics, presenting several key benefits. Unlike antibiotics, which can disrupt the natural balance of bacteria in the urinary tract, probiotics help bolster the body's innate defense mechanisms against harmful bacteria. This

distinction is especially important as we deepen our understanding of the urinary microbiome and its crucial role in maintaining urinary health (78). Probiotic treatments, especially those enriched with *Lactobacillus* and *Bifidobacterium* strains, weave a fascinating tapestry of action when it comes to preventing and managing urinary tract infections (UTIs). These friendly bacteria create a haven for health by producing lactic acid, which helps to keep the urinary pH in an ideal range, hindering the growth of unwanted pathogens. Moreover, they engage in a clever battle, vying for precious adhesion spots on the urethral and bladder lining, effectively safeguarding against the invasion of uropathogenic organisms. This harmonious interplay highlights the power of probiotics as natural defenders in our bodies (79). The remarkable ability of probiotic strains to produce antimicrobial substances significantly boosts their protective qualities. One of the standout benefits of probiotic therapy is its exceptional safety compared to antibiotics. While the latter can often cause unwanted side effects and foster the rise of antibiotic-resistant bacteria, probiotics are gentle on the system, exhibiting minimal adverse reactions and steering clear of promoting resistance. This unique advantage becomes especially crucial in the battle against recurrent urinary tract infections (UTIs), where reliance on antibiotics can lead to tougher, more resilient infections and upset the delicate balance of our microbiota (30). While antibiotics are designed to tackle active infections, probiotics provide ongoing protection by helping to maintain a healthy microbial balance. This preventative approach can play an important role in reducing the likelihood of recurrent infections and minimizing the need for multiple rounds of antibiotics. Patients often prefer probiotic treatments, thanks to their natural ingredients and superior safety profile, which can lead to better adherence to treatment plans. Additionally, probiotics can be effectively integrated into comprehensive treatment regimens, allowing for the combination with other non-antibiotic options. This offers flexibility in treatment approaches and supports more personalized care strategies (79). Current research into probiotics is certainly encouraging, but it's clear that we

still have some ground to cover. To truly harness their benefits in managing urinary tract infections we need robust clinical trials that can cement standardized protocols and confirm their effectiveness. Researchers are diving deep into finding the most effective bacterial strains, optimized dosage regimens, and the best delivery methods to unlock the full therapeutic potential of probiotics (80).

8. Future Directions and Innovations

The realm of probiotic treatment for urinary tract infections (UTIs) is brimming with exciting possibilities and groundbreaking innovations. As we delve further into this changing landscape, next-generation sequencing and advanced culturing techniques are revolutionizing our comprehension of the bladder's microbiome. This newfound knowledge paves the way for more precise probiotic therapies tailored to individual needs (81). A particularly intriguing avenue involves creating multi-strain probiotic combinations, especially those that harness the strengths of various *Lactobacillus* and *Bifidobacterium* species, to facilitate synergistic therapeutic benefits. Moreover, the advent of specialized drug delivery systems aimed specifically at the urinary tract holds remarkable promise. These innovations seek not only to boost the survival rates of beneficial bacteria but also to maximize their therapeutic impact. Another captivating area of study is the fusion of biofilm-disrupting technologies with probiotic treatments (82). In addition, advancements in microencapsulation techniques and targeted delivery mechanisms are being fine-tuned to significantly improve the resilience and effectiveness of probiotic strains during treatment. When combined with ongoing exploration into how bacteria adhere and colonize, these cutting-edge developments could herald a new era of more effective strategies for combating urinary tract infections, ultimately reducing our dependency on traditional antibiotics. The future looks bright for probiotics as we explore uncharted territories in UTI management (83, 84).

9. Conclusion

Recurrent UTIs significantly reduce the quality of life, and while antibiotic prophylaxis is useful dur-

ing treatment, it may also promote resistance to uropathogens. Despite the paucity of research on antibiotic-free recurrent UTI prevention in recent years, interest in this topic has grown. This interest stems from a desire to be treated with natural materials, whereas doctors are concerned about antibiotic resistance. However, there is currently insufficient data to support the use of probiotics. The majority of published research on the use of probiotics in the treatment and prevention of UTIs have low scientific value, and the treatment regimens used are inconsistent and time-consuming. Patients choose probiotics over antibiotics because they are safer and more comfortable. In clinical practice, the significance of patient preferences in treatment decisions cannot be emphasized. This, combined with a lack of documented therapy recommendations and varied success rates among patients, is prompting the use of probiotics as part of multi-modal therapies for multifactorial disorders such as recurrent UTIs.

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