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Reveiw Article

The Power of Probiotics to Combat Urinary Tract Infections: A Comprehensive Review

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ABSTRACT

Urinary tract infections (UTIs) are among the most common bacterial infections and can cause significant morbidity, particularly in women. Recurrent UTIs are a significant clinical problem, and current prophylactic measures, such as antibiotics, are associated with side effects and the risk of antimicrobial resistance. Probiotics, defined as live microorganisms that confer health benefits to the host, have emerged as a potential alternative to traditional treatments for recurrent UTIs.

Probiotics can act by modulating the host's immune system, competitively excluding uropathogens, and producing antibacterial substances, such as bacteriocins. Clinical evidence supports the use of probiotics as a safe and effective intervention for the prevention and treatment of recurrent UTIs. However, selecting appropriate probiotic strains for UTIs can be challenging, and the safety and efficacy of probiotics depend on the strain, dosage, and timing of administration.

The safety profile of probiotics is generally excellent, and side effects are usually mild and self-limiting. However, certain populations, such as immunocompromised and critically ill patients, may be at increased risk of adverse events, and caution should be exercised when considering probiotic use in these populations. Strategies for ensuring probiotic safety and efficacy include adherence to good manufacturing practices, rigorous testing for the presence of contaminants, and standardization of dosing and administration protocols.

Despite the potential of probiotics for the prevention and treatment of recurrent UTIs, several challenges and limitations remain. These include limited access to high-quality probiotic products, challenges in selecting appropriate strains, and lack of consensus regarding optimal dosing and duration of probiotic use. Future research should focus on identifying optimal probiotic strains and regimens for the prevention and treatment of UTIs, understanding the role of gut microbiota in urogenital health, and developing new probiotic technologies and delivery methods.

1. Introduction

1.1. Urinary tract infections

Urinary tract infections (UTIs) are among the prevalent bacterial infections worldwide, with a significant impact on both individual health and healthcare costs[1]. They occur when bacteria, usually from the intestinal microbiota, enter the urinary tract and multiply, causing inflammation and tissue damage[2]. The UTIs can happen in any part of the urinary system, from the bladder to the kidneys, and can range in severity from mild discomfort to life-threatening sepsis[2]. Women are at higher risk of UTIs than men, due to anatomical and hormonal factors, and recurrent UTIs are a common problem, affecting up to 25% of women who experience an initial UTI[3].

The most common causative agent of UTIs is Escherichia coli (*E. coli*), a gram-negative bacterium that colonizes the rectal and perineal areas[4]. Other bacteria that can cause UTIs include *Klebsiella pneumoniae*, *Proteus*

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mirabilis, and *Staphylococcus saprophyticus*[4]. Risk factors for UTIs include female gender, sexual activity, use of spermicides or diaphragms, urinary tract abnormalities, and impaired immune function. The UTIs can also be caused by catheterization or other medical procedures introducing bacteria into the urinary tract[3,4].

Antibiotics are the mainstay of UTI treatment, but the emergence of antibiotic-resistant strains of bacteria has led to increasing interest in alternative approaches, such as probiotics[5]. Probiotics are live microorganisms that confer health benefits when consumed in adequate amounts[5]. They can help prevent UTIs by competing with pathogenic bacteria for resources, producing antibacterial substances, and modulating the host immune response[6]. Probiotics can also be used as a treatment for UTIs, either alone or in combination with antibiotics[7]. While there is growing evidence for the efficacy of probiotics in preventing and treating UTIs, challenges remain in determining the optimal probiotic strains, dosages, and administration routes, as well as ensuring their safety and quality[6,7].

1.2. The role of probiotics in the prevention and treatment of urinary tract infections

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits to the host[8]. They are commonly found in fermented foods and dietary supplements and can contain various bacterial and fungal species[8]. Probiotics can exert their effects through several mechanisms, including direct competition with pathogenic bacteria for resources, antibacterial substances production, and host immune response modulation. The use of probiotics to prevent and treat UTIs has gained increasing attention due to the limitations of conventional antibiotic therapy[9].

The mechanisms by which probiotics can prevent UTIs include the production of antimicrobial peptides, modulation of the host immune response, and the ability to compete with pathogenic bacteria for adherence to the urinary tract mucosa[9,10]. *Lactobacilli* and *Bifidobacteria* are two of the most commonly studied probiotic strains for UTI prevention, as they are natural colonizers of the human gut and vaginal microbiota[10]. These strains have been indicated to produce hydrogen peroxide, which can inhibit the growth of uropathogenic bacteria, and to enhance mucus production in the urinary tract, which can physically prevent bacterial adhesion[10].

Probiotics can also be used as an adjunct to antibiotic therapy for treating UTIs, as they can help replenish the normal microbiota and reduce the risk of recurrent infections[11]. One study found that using *Lactobacillus crispatus* vaginal suppositories in combination with antibiotics was associated with a lower risk of recurrent UTIs compared to antibiotic therapy alone[11]. Another study indicated that the use of *Lactobacillus rhamnosus* (*L. rhamnosus*) GG reduced the risk of antibiotic-associated diarrhea and other adverse effects in patients with UTIs[12]. However, further investigation is required to determine the optimal probiotic strains, dosages, and administration routes for UTI treatment.

1.3. Purpose of study

The purpose of this study is to provide a comprehensive overview of the current knowledge regarding the apply of probiotics for the prevention and treatment of urinary tract infections (UTIs). The article will begin with background information on UTIs, including their causes, risk factors, and current treatment options. The definition of probiotics and their role in the prevention and treatment of UTIs will then be discussed, focusing on the mechanisms by which probiotics can prevent and treat UTIs, as well as the most commonly studied probiotic strains. In addition, the safety and quality of probiotic supplements will also be discussed, as well as the potential of probiotics to reduce the use of antibiotics and the emergence of antibiotic-resistant bacteria will be explored, as well as the economic implications of probiotic therapy for UTIs. The information provided in this review will be of interest to researchers, clinicians, and patients seeking to optimize their UTI prevention and treatment strategies.

2. Pathogenesis of urinary tract infections

2.1. Overview of urinary tract infections-causing pathogens

The majority of UTIs are caused by uropathogenic *E. coli* (UPEC), which can colonize and invade the urinary tract epithelium, leading to inflammation and tissue damage[1]. Other common UTI-causing pathogens include *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterococcus faecalis*[2]. The virulence factors of these pathogens, including adhesins, toxins, and iron-acquisition systems, are critical for colonization, invasion, and persistence in the urinary tract[2,4].

Uropathogenic *E. coli* is the most common cause of UTIs, accounting for over 80% of community-acquired UTIs[13]. The UPEC strains are genetically diverse and can express various virulence factors, including pili, fimbriae, and adhesins, that allow them to attach to and invade host cells[13]. The UPEC also produce toxins and iron acquisition systems that enable them to persist and cause inflammation in the urinary tract[4,13]. Several studies have identified specific UPEC virulence factors associated with increased UTI severity and recurrence, including the P fimbriae and S fimbriae[2,4,13].

Klebsiella pneumoniae is another common cause of UTIs, particularly in hospitalized patients and those with underlying medical conditions[2]. The *K. pneumoniae* strains can produce a range of virulence factors, including adhesins, capsule polysaccharides, and iron-acquisition systems, that enable them to colonize and cause infections in the urinary tract[14]. Proteus mirabilis is a common cause of catheter-associated UTIs and is characterized by its ability to swarm across surfaces and form biofilms[15]. *Enterococcus faecalis* is a less common UTI pathogen associated with recurrent infections and resistance to multiple antibiotics[16]. Understanding the virulence factors and pathogenic mechanisms of these UTI-causing pathogens is critical for developing effective prevention and treatment strategies, including probiotics.

2.2. Pathogenesis of urinary tract infections

Understanding the pathogenesis of UTIs is critical for the development of effective prevention and treatment strategies[2]. Adhesion, colonization, and biofilm formation are important mechanisms by which pathogenic bacteria cause UTIs[2,4]. Adhesion to the urinary tract epithelium is the first step in the pathogenesis of UTIs. Adhesion is mediated by adhesins on the bacterial surface, which bind to specific receptors on the urinary tract epithelial cells. Adhesins can be expressed on fimbriae, pili, or other surface structures, and environmental signals can regulate their expression. The initial adhesion of bacteria to the urinary tract epithelium is a critical step in the pathogenesis of UTIs, as it allows bacteria to evade the host immune response and establish a foothold in the urinary tract[2,4].

Once bacteria have adhered to the urinary tract epithelium, they can colonize the urinary tract and initiate an inflammatory response[2]. The expression of virulence factors, including iron acquisition systems and adhesins, facilitates colonization[4]. Iron is an necessary nutrient for bacterial growth, and the urinary tract is a relatively iron-poor environment. Pathogenic bacteria express iron acquisition systems, including siderophores, which enable them to scavenge iron from the host[2,4]. Adhesins are critical for bacterial colonization, allowing bacteria to attach to and invade host cells[4]. Bacterial colonization of the urinary tract can lead to tissue damage and inflammation, which can cause symptoms of UTIs, including dysuria and urinary frequency[2,4].

Biofilm formation is an important mechanism by which bacteria can persist in the urinary tract and resist antimicrobial therapy[17]. Biofilms are complex bacteria communities encased in a matrix of extracellular polymeric substances[18]. Biofilms can form on the surface of urinary catheters, stones, or damaged urinary tract tissue, and are resistant to antibiotics and the host immune response[18]. Biofilm formation is mediated by a range of virulence factors, including polysaccharide adhesins, and is regulated by environmental signals[17]. The formation of biofilms can lead to persistent infections and recurrent UTIs, making them a significant clinical challenge[17,18].

2.3. Antibiotic resistance and its implications on urinary tract infections

Antibiotic resistance is a significant global health challenge that has important implications for the treatment of urinary tract infections (UTIs)[6]. The emergence and spread of antibiotic-resistant bacteria have been driven by a range of factors, including the overuse and misuse of antibiotics, as well as the spread of resistance genes through horizontal gene transfer[19]. Antibiotic resistance can make UTIs more difficult to treat, as bacteria become resistant to commonly used antibiotics[19].

Resistance to antibiotics used to treat UTIs is a growing concern, as many of the bacteria that cause UTIs have developed resistance to multiple antibiotics[6,19]. This has led to a significant inhance in the use of broad-spectrum antibiotics, which can have serious side effects and contribute to the development of antibiotic resistance[19]. In addition, the overuse of antibiotics has been associated with the disruption of the gut microbiota, which can lead to several health problems, including the development of antibiotic-resistant infections[20].

The rise of antibiotic-resistant UTIs has significant clinical implications, as it can lead to treatment failure, prolonged hospitalization, and increased healthcare costs[20]. Treatment options for antibiotic-resistant UTIs are limited and may include the use of combination therapy, higher doses of antibiotics, or the use of last-line antibiotics[6]. These options are associated with significant risks and side effects, and may contribute to developing further antibiotic resistance[19]. In addition, there is a need for alternative approaches to the prevention and treatment of UTIs that do not rely on antibiotics[20].

3. Probiotics for the prevention of urinary tract infections

3.1. Mechanisms of action

The mechanisms of action of probiotics in preventing UTIs are multifactorial and involve a range of host and bacterial factors[21]. Probiotics can compete with uropathogens for nutrients and adhesion sites, produce bacteriocins that inhibit the growth of pathogenic bacteria, and modulate the host immune response[9]. In addition, probiotics can restore the balance of the gut and vaginal microbiota, which can protect uropathogens[9].

Probiotics are effective in preventing UTIs by inhibiting the adhesion and colonization of uropathogens in the urinary tract[9,21]. Several studies have indicated that probiotics can interfere with the adhesion of uropathogenic *E. coli* (UPEC) to uroepithelial cells, which is a critical step in the development of UTIs[22]. Probiotics can also prevent the formation of biofilms by UPEC, which can increase their resistance to antibiotics and immune defenses[23]. By inhibiting the adhesion and colonization of uropathogens, probiotics can reduce the risk of UTIs[22,23].

Probiotics can also modulate the host immune response, which plays an important role in preventing UTIs[9]. Probiotics can enhance the production of immunoglobulins, cytokines, and other immune factors involved in the defense against uropathogens[9]. In addition, probiotics can downregulate the production of pro-inflammatory cytokines, contributing to the development of UTIs[24]. By modulating the host immune response, probiotics can provide protection against UTIs and reduce the severity of infections[9,24].

The restoration of the gut and vaginal microbiota by probiotics is another mechanism by which they can prevent UTIs[25]. Disruption of the gut and vaginal microbiota can lead to dysbiosis, which can increase the risk of UTIs[25]. Probiotics can restore the balance of the gut and vaginal microbiota, which can provide protection against uropathogens[25]. In addition, probiotics can produce lactic acid, which can decrease the pH of the urine and inhibit the growth of uropathogens[24,25]. The restoration of the gut and vaginal microbiota by probiotics is a promising approach for the prevention of UTIs, as it targets the underlying causes of UTIs[25].

3.2. Clinical evidences

Clinical studies have demonstrated the efficacy of specific probiotic strains in reducing the incidence of UTIs[9]. *Lactobacillus crispatus* and *L. rhamnosus* have been the most widely studied strains for this purpose[12,21].

The mechanism by which probiotics prevent UTIs is multifactorial[26]. Probiotics have been indicated to modulate the host immune response, maintain a low vaginal pH, and produce bacteriocins that inhibit the growth of uropathogens[9]. In addition, probiotics are able to compete with uropathogens for adhesion sites on uroepithelial cells, preventing colonization and subsequent infection[21]. While further study is necessary to comprehend the mechanisms of action fully, the clinical evidence suggests that probiotics significantly decrease the incidence of UTIs[9,21,26].

In a randomized, double-blind, placebo-controlled trial, the use of a probiotic mixture containing *Lactobacillus acidophilus*, *L. rhamnosus*, and *Streptococcus thermophilus* (*S. thermophilus*) reduced the incidence of UTIs in women with recurrent UTIs[27]. In another study, daily intake of *Lactobacillus crispatus* CTV-05 reduced the risk of recurrent UTIs in premenopausal women[28]. Similarly, the use of *L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 reduced the incidence of UTIs in postmenopausal women[29].

Overall, the clinical evidence strongly supports the use of probiotics in the prevention of UTIs[9,21,26]. While further studies are needed to establish optimal dosages and formulations, probiotics have the potential to significantly reduce the burden of UTIs and limit the overuse of antibiotics in this context. It is important, however, to identify the specific strains and doses of probiotics that are most effective for UTI prevention, as not all probiotics are equally effective in this regard [30].

3.3. Potential probiotics for prevention of urinary tract infections

Several bacterial strains have been explored for their potential to prevent UTIs, with *Lactobacillus* species being the most commonly studied[21,27].

Lactobacillus is one of the most commonly studied probiotic strains for UTI prevention, and is effective in decreasing the incidence of UTIs in some studies[27]. Other strains of probiotics that have been studied for their potential to prevent UTIs include *Bifidobacterium*, *Streptococcus*, and *Enterococcus*, among others[31,32]. These strains have been found to prevent the growth of uropathogenic bacteria, prevent biofilm formation, and stimulate immune responses that can help prevent UTIs[32]. *Lactobacillus crispatus* is a strain of *Lactobacillus* that is particularly effective in preventing UTIs[10]. Studies have found that women with a healthy vaginal microbiome, including high levels of *Lactobacillus crispatus*, are less likely to experience UTIs[10]. *Lactobacillus crispatus* has been indicated to inhibit the growth of uropathogenic bacteria and promote the growth of beneficial bacteria that can help prevent UTIs[10].

Another promising bacterial strain for UTI prevention is *E. coli* Nissle 1917 (EcN)[33]. This strain has been extensively studied and has been shown to have a range of beneficial effects on the host immune system, including modulation of cytokine production, promotion of mucosal barrier function, and enhancement of innate and adaptive immune responses. In addition, EcN has been indicated to effectively inhibit uropathogenic *E. coli* through the secretion of microcins, which are small antimicrobial peptides that specifically target and kill related strains[33].

Other bacterial strains that have indicated potential for UTI prevention include *Bifidobacterium* species, which are commonly used in probiotic supplements for digestive health, and *S. thermophilus*, a commonly used yogurt starter culture[34]. *Bifidobacterium* species have been indicated to decrease the risk of UTIs in postmenopausal women, and *S. thermophilus* has been indicated to inhibit the adhesion of uropathogenic *E. coli* to bladder cells. These strains, along with others such as *Enterococcus faecalis* and *Propionibacterium freudenreichii*, represent promising candidates for further investigation in the prevention of UTIs[34].

In addition to these specific probiotic strains, multi-strain probiotic supplements have also been studied for their potential to prevent UTIs[10]. These supplements typically contain a combination of *Lactobacillus* and *Bifidobacterium* strains, as well as other beneficial bacteria. Studies have found that multi-strain probiotics can be effective in reducing the incidence of UTIs in women with a history of recurrent UTIs[10].

4. Probiotics for the treatment of urinary tract infections

4.1. Mechanisms of action

The mechanisms of action of probiotics in treating UTIs include the production of antibacterial compounds, competitive inhibition, and immunomodulation[8,9]. Probiotics have been indicated to produce antibacterial compounds, such as organic acids and bacteriocins, which can inhibit the growth of uropathogens[35]. *Lactobacillus crispatus* has been found to produce hydrogen peroxide, which can kill uropathogenic bacteria. *Lactobacillus acidophilus* and *L. rhamnosus* have been indicated to produce bacteriocins that can inhibit the growth of uropathogenic bacteria[8,10]. Probiotics can also compete with uropathogens for adhesion to uroepithelial cells and thereby prevent their colonization. *Lactobacilli* and *Bifidobacteria* can also acidify the urine, which can reduce the risk of UTI[8,34].

In addition to producing antibacterial compounds and competitive inhibition, probiotics can also modulate the immune response[36]. Probiotics can increase the production of immunoglobulins, such as IgA, which can bind to uropathogens and prevent their adhesion to uroepithelial cells[36]. Probiotics can also activate macrophages, natural killer cells, and neutrophils, which can kill uropathogens[37]. Furthermore, probiotics can modulate the balance of T-helper cells, increasing the number of T-helper 1 cells, which produce interferon-gamma, a cytokine that can kill uropathogens [37].

Several clinical studies have investigated the use of probiotics in treating UTIs[7-10]. A randomized controlled trial found that a probiotic containing *Lactobacillus crispatus* reduced the recurrence of UTIs in women[28]. Another study found that a probiotic containing *L. rhamnosus* and *Lactobacillus reuteri* reduced the incidence of UTIs in premenopausal women. In addition, a meta-analysis of 10 randomized controlled trials found that probiotics were effective in preventing UTIs[10].

While the use of probiotics as an alternative therapy for UTIs is promising, there are still several challenges that need to be addressed. The optimal probiotic strain, dose, and duration of therapy need to be determined. In addition, the safety and efficacy of probiotics need to be established in larger, randomized, controlled trials. Overall, the use of probiotics as a potential alternative to antibiotics for the treatment of UTIs warrants further investigation[6-10].

4.2. Clinical evidences

Probiotics are emerging as a promising alternative to antibiotics in the prevention and treatment of UTIs[6]. While the mechanisms by which probiotics exert their beneficial effects are still being elucidated, several clinical studies have provided evidence supporting their use in UTI treatment[6].

In a randomized, double-blind, placebo-controlled study, female patients with recurrent UTIs were given *Lactobacillus crispatus* CTV-05, a probiotic strain isolated from the vagina[38]. The study found that the probiotic group had a significantly lower incidence of UTIs compared to the placebo group[38]. Another clinical trial investigated the efficacy of the probiotic combination of *L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 in the treatment of acute UTIs[39]. The probiotic group showed a higher rate of resolution of symptoms and bacterial eradication compared to the placebo group[39].

A study by Beerepoot et al. showed that daily oral administration of *L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 in women with recurrent UTIs led to a decrease in the incidence of UTIs compared to placebo. This study involved a randomized, double-blind, placebo-controlled trial of 252 women, and the results showed that the use of probiotics reduced the risk of UTIs by approximately 50%[40].

Another clinical study by Stapleton et al. investigated the use of oral *Lactobacillus crispatus* in premenopausal women with a history of recurrent UTIs[41]. The results showed a significant reduction in the recurrence rate of UTIs in the probiotic group compared to the placebo group[41]. The authors concluded that oral probiotics are a safe and effective alternative for the prevention of UTIs in women[41].

A recent systematic review and meta-analysis by Gao et al. also supported the use of probiotics for the treatment of UTIs. This study evaluated the efficacy of probiotics for the treatment of UTIs and included 11 randomized controlled trials with a total of 1,507 patients[42]. The results indicated that the use of probiotics was associated with a significant reduction in the incidence of recurrent UTIs[42].

In addition to the studies above, a recent study by Khalesi et al. found that oral probiotics were effective in reducing the recurrence of UTIs in women with a history of UTIs[43]. This randomized controlled trial included 120 women and found that the use of *Lactobacillus acidophilus* and *Bifidobacterium lactis* reduced the incidence of UTIs by 45.7%[43].

Another study by Czaja et al. evaluated the use of a vaginal probiotic containing *Lactobacillus crispatus* in women with recurrent UTIs[44]. The results showed that the probiotic group had a lower incidence of UTIs compared to the control group. The authors suggested that the use of vaginal probiotics may be an effective way to prevent UTIs in women[44].

Furthermore, in vitro studies have shed light on the mechanisms by which probiotics prevent and treat UTIs[6,8]. Probiotics have been indicated to compete with uropathogens for adherence to uroepithelial cells, effectively preventing the pathogens from colonizing the urinary tract. Probiotics can also modulate the host immune response, which plays a key role in the pathogenesis of UTIs[8,34]. For example, some probiotic strains have been indicated to decrease the expression of cytokines and chemokines that recruit immune cells to the urinary tract, thereby enhancing the host's ability to fight off infections[34].

While the clinical evidence supporting the use of probiotics in UTI treatment is promising, further studies are needed to elucidate the optimal dosing and strain selection[7,8]. Additionally, the use of probiotics as a stand-alone treatment for UTIs may not be effective in all cases, and they may need to be used in combination with antibiotics or other treatments[7,8]. Nonetheless, the use of probiotics as a complementary or alternative approach to UTI treatment holds great promise, particularly in light of the rising rates of antibiotic resistance[7-10].

4.3. Potential probiotic strains for treatment of urinary tract infections

Many strains of probiotics have been investigated for their potential to treat UTIs[7-10]. One strain that has indicated promise in clinical studies is *Lactobacillus crispatus*[8]. In a study of premenopausal women with recurrent UTIs, daily oral intake of a L. crispatus probiotic was associated with a significant reduction in the frequency of UTIs[8,10]. Another strain that has been studied is *Lactobacillus fermentum*. In a randomized controlled trial of postmenopausal women with recurrent UTIs, daily intake of a L. fermentum probiotic was associated with a significant decrease in the incidence of UTIs[10]. However, more research is needed to determine the optimal dose and duration of treatment with these strains.

Another promising strain for UTI treatment is *L. rhamnosus* GR-1[39]. In a double-blind, placebo-controlled trial of women with acute UTIs, treatment with a combination of *L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 was associated with a higher rate of clinical cure and a lower rate of recurrence compared to placebo[39]. Similarly, a study of pregnant women found that treatment with *L. rhamnosus* GR-1 and *L. reuteri* RC-14 was associated with a lower incidence of UTIs compared to placebo[40].

Bifidobacterium bifidum is another probiotic strain that has indicated potential for UTI treatment[10,31,32]. In a study of premenopausal women with recurrent UTIs, daily intake of a probiotic containing *B. bifidum* was associated with a lower incidence of UTIs compared to placebo[32]. Additionally, a randomized controlled trial of women with acute uncomplicated cystitis found that treatment with a combination of *B. bifidum* and *L. acidophilus* was associated with a higher rate of clinical cure than a placebo[31,32].

Other probiotic strains that have been investigated for their potential to treat UTIs include *S. thermophilus*, *Enterococcus faecalis*, and *Bifidobacterium lactis*[34]. However, more research is needed to determine their efficacy in treating UTIs.

5. Probiotics for the prevention and treatment of recurrent urinary tract infections

5.1. Definition and epidemiology

Recurrent urinary tract infections (rUTIs) are defined as two or more UTIs within six months or three or more UTIs within one year[45]. The rUTIs affect a substantial number of women and are a significant public health concern, leading to substantial morbidity and healthcare costs[45]. The incidence of rUTIs in young, healthy women is estimated to be around 25%, with up to 50% of these women experiencing additional UTIs[46]. In postmenopausal women, the incidence of rUTIs increases, with up to 50% of women experiencing rUTIs[46].

Recurrent UTIs are a multifactorial condition that is often associated with host factors, such as age, gender, genetics, and underlying medical conditions, as well as bacterial virulence factors[45]. Among the bacterial virulence factors that contribute to rUTIs are the formation of biofilms, the expression of adhesive structures, and the acquisition of antibiotic resistance[47]. Biofilm formation by uropathogenic bacteria may play a particularly important role in the pathogenesis of rUTIs[47]. The biofilm matrix provides protection against antibiotics and the host immune system, allowing the bacteria to persist in the urinary tract and cause recurrent infections[47].

Recurrent UTIs are typically treated with antibiotics, but the emergence of antibiotic-resistant strains often limits this approach[46,47]. Moreover, repeated courses of antibiotics can lead to alterations in the urinary microbiome, potentially increasing the risk of rUTIs[46,47]. Alternative approaches to the prevention and treatment of rUTIs are therefore needed. Probiotics are a promising intervention for preventing and treating rUTIs, as they can restore the normal urogenital microbiota and inhibit the growth and virulence of uropathogenic bacteria[45].

5.2. Mechanisms of action

The mechanisms by which probiotics exert their effects in preventing and treating rUTIs are not fully understood. However, they involve several factors, including the microbiota modulation, the production of antibacterial compounds, and the strengthening of the epithelial barrier[38].

One of the key mechanisms by which probiotics may prevent rUTIs is by modulating the gut and vaginal microbiota[48]. Dysbiosis in the vaginal microbiota, characterized by a reduction in *Lactobacillus* species and an overgrowth of pathogenic bacteria, has been associated with an increased risk of UTIs. Probiotics can help restore the normal vaginal microbiota and prevent the overgrowth of pathogenic bacteria[48]. The use of probiotics may also help prevent the spread of uropathogens from the gut to the urinary tract, as some probiotic strains have been indicated to colonize the gut and vagina and compete with uropathogenic bacteria for resources[48].

Another mechanism by which probiotics may prevent rUTIs is through the production of antibacterial compounds, such as organic acids and bacteriocins[49]. These compounds can inhibit the growth of uropathogenic bacteria and prevent them from colonizing the urinary tract[49]. Probiotic strains have also been indicated to induce the production of host antimicrobial peptides, such as defensins, which can enhance the innate immune response to infection and help prevent the recurrence of UTIs[49].

In addition to their preventative effects, probiotics may also effectively treat rUTIs. Several studies have indicated that the use of probiotics as an adjunct to antibiotics can improve the clinical outcomes of UTIs, including reducing the incidence of recurrent infections[38]. This may be due in part to the ability of probiotics to enhance the efficacy of antibiotics by reducing the potential for antibiotic resistance and promoting the clearance of uropathogens. Probiotics may also enhance the immune response to infection, and reduce the risk of complications associated with rUTIs, such as pyelonephritis and sepsis[38,48].

5.3. Clinical evidences

Clinical evidence supporting the use of probiotics for rUTIs is steadily increasing[45,46]. A meta-analysis of randomized controlled trials (RCTs) assessing the effectiveness of probiotics for preventing rUTIs found that probiotics significantly reduced the risk of rUTIs, compared to placebo or no treatment[38]. Several RCTs have also reported a decrease in the number of UTIs and a decrease in antibiotic use in participants who took probiotics compared to those who did not. However, the optimal dose, frequency, and duration of probiotic supplementation are not yet well established, and more research is needed to address these issues[38,45,46].

The mechanisms of action by which probiotics prevent rUTIs are not completely understood, but they likely involve several factors[47]. Probiotics may improve the composition and function of the vaginal and gut microbiota, which can affect the vaginal and urinary microbiota[47]. Additionally, probiotics may produce antimicrobial substances that inhibit the growth of uropathogenic bacteria, or they may compete with uropathogens for nutrients and adhesion sites in the urinary tract[45]. Probiotics may also modulate the host immune response to prevent colonization by uropathogens[47].

5.4. Potential probiotic strains for recurrent urinary tract infections

As described earlier, recurrent UTIs can be challenging to treat with antibiotics, as the bacteria can develop resistance and the immune system may be unable to clear the infection[38]. Probiotics may offer a promising alternative or adjunct therapy, as they can help restore the natural balance of microorganisms in the urinary tract and enhance the body's defenses against infection[38,45]. There are several potential probiotic strains that have been studied for their effectiveness in preventing and treating recurrent UTIs[38,47,48].

One potential probiotic strain is *Lactobacillus crispatus* (*L. crispatus*), which is a common inhabitant of the healthy vaginal microbiota and has been indicated to be associated with a lower risk of UTIs[48]. Studies have indicated that oral or intravaginal administration of *L. crispatus* can reduce the incidence and recurrence of UTIs, as well as decrease the severity of symptoms[48]. This strain may work by promoting the growth of beneficial bacteria in the urinary tract, stimulating the immune system, and producing antimicrobial compounds[48].

Another potential probiotic strain for recurrent UTIs is *Lactobacillus rhamnosus GR-1*, which has been indicated to be effective in preventing and treating various types of infections[39,40]. This strain may work by adhering to the epithelial cells of the urinary tract and preventing the attachment and growth of pathogenic bacteria, as well as modulating the immune response and producing antimicrobial substances. Studies have indicated that oral administration of *L. rhamnosus GR-1* can significantly reduce the incidence and severity of UTIs[39,40].

Bifidobacterium longum has also been studied as a potential probiotic strain for recurrent UTIs, as it is a common inhabitant of the gut microbiota and has been indicated to have immunomodulatory and antimicrobial properties[31,32]. Studies have indicated that oral administration of *B. longum* can significantly reduce the incidence and severity of UTIs, as well as increase the levels of beneficial bacteria in the urinary tract[31,32]. This strain may work by modulating the host immune response and producing bacteriocins and other antimicrobial compounds[31,32].

Finally, *S. thermophilus* is another potential probiotic strain for recurrent UTIs, as it has been indicated to have immunomodulatory and antimicrobial properties. Studies have shown that oral administration of *S. thermophilus* can significantly reduce the incidence and severity of UTIs, as well as increase the levels of beneficial bacteria in the urinary tract[34]. This strain may work by modulating the host immune response and producing bacteriocins and other antimicrobial compounds[34].

6. Safety and potential side effects of probiotics

6.1. Safety of probiotics

Probiotics are live microorganisms that provide health benefits when consumed in adequate amounts[9]. While probiotics have gained widespread attention for their potential to prevent and treat UTIs, their safety profile is a crucial consideration[28]. The safety of probiotics is generally considered to be favorable, although it is important to assess potential risks associated with their use[50].

Studies have suggested that probiotics are associated with a low risk of adverse effects, with most adverse events being mild and self-limiting[9,10]. The majority of adverse events reported with probiotic use are related to gastrointestinal symptoms such as flatulence, bloating, and abdominal discomfort. However, these symptoms typically resolve within a few days and are not considered serious[50].

The safety of probiotics is also affected by the type of strain used, as different strains can have different effects on the body[50]. Some probiotic strains have been associated with more severe adverse events, particularly in individuals with compromised immune systems[50]. For this reason, it is important to carefully select the strain of probiotic used, as well as to assess the risk of potential adverse events in different populations, such as immunocompromised individuals or infants[50,51].

The use of probiotics in the prevention and treatment of UTIs has been indicated to be generally safe, with a low risk of adverse events. In a systematic review and meta-analysis of randomized controlled trials, probiotics were found to be generally safe and well-tolerated, with no serious adverse events reported[51]. Another systematic review of studies examining the use of probiotics for the prevention of UTIs also reported a low incidence of adverse events associated with probiotic use[52].

6.2. Side effects and risk factors associated with probiotics

Although generally considered safe, probiotics may be associated with certain side effects and risks, particularly in individuals with compromised immune systems or underlying medical conditions[53].

The most common side effects associated with probiotic use are gastrointestinal disturbances, such as bloating, gas, and diarrhea[54]. These side effects are generally mild and self-limited and tend to resolve with continued use of the probiotic. However, in some cases, particularly in individuals with weakened immune systems, probiotic use may lead to serious infections, such as sepsis or endocarditis[54].

Another potential risk associated with probiotic use is the risk of antibiotic resistance[6]. Some studies have suggested that certain strains of probiotics may acquire resistance genes from other bacteria in the gut, potentially leading to the development of antibiotic-resistant strains[6]. This is particularly concerning in the context of recurrent UTIs, often treated with antibiotics[6].

In addition to these risks, there have also been reports of probiotic-induced infections, particularly in individuals with compromised immune systems[53]. For example, a study described a patient with acute pancreatitis who developed sepsis after taking a probiotic supplement containing *Lactobacillus rhamnosus GG*[53]. Although such cases are rare, they underscore the importance of caution when using probiotics, particularly in vulnerable populations.

It is worth reiterating twice that the safety of probiotics may vary depending on the specific strain and formulation used[55]. For example, a study of a probiotic supplement containing *Lactobacillus casei* found that it was associated with an increased risk of acute pancreatitis in a small number of patients[55]. Therefore, it is important to carefully consider the risks and benefits of individual probiotic supplements before use, particularly in individuals with underlying medical conditions or compromised immune systems.

6.3. Strategies for ensuring probiotic safety and efficacy

The use of probiotics is generally considered safe, but there are still concerns about their safety and efficacy, particularly in vulnerable populations such as critically ill patients, infants, and the elderly[50]. Therefore, several strategies have been proposed to ensure the safety and efficacy of probiotics, such as using probiotic strains that have been extensively studied and have a good safety record, and monitoring for adverse effects during use.

One strategy for ensuring probiotic safety is to use well-characterized probiotic strains that have been extensively studied in human trials[50]. For example, the strain *Lactobacillus rhamnosus GG* has been used in many clinical trials and has a long safety record, making it a reliable choice for probiotic supplementation[53]. Other strains, such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, have also been extensively studied and are considered safe for use in humans[31,32].

Another strategy for ensuring probiotic safety is to monitor for adverse effects during use[56]. Although probiotics are generally well-tolerated, adverse effects such as gastrointestinal upset, allergic reactions, and infections have been reported in some cases[56]. Therefore, monitoring for adverse effects during probiotic supplementation is important to identify and manage any potential safety concerns.

Prebiotics can also be used to improve the safety and efficacy of probiotics[57]. Prebiotics are non-digestible carbohydrates that selectively stimulate the growth and activity of beneficial bacteria in the gut, including probiotics[57]. By providing a favorable environment for probiotic growth and activity, prebiotics can enhance the efficacy of probiotic supplementation and reduce the risk of adverse effects[57].

Formulation and delivery methods can also influence the safety and efficacy of probiotics[58]. Different formulations, such as capsules, tablets, and powders, may have different effects on the survival and viability of probiotic strains, as well as their release and colonization in the gut[58]. Therefore, choosing the appropriate formulation and delivery method is important for ensuring the safety and efficacy of probiotics.

Finally, regulatory oversight is important for ensuring the safety and efficacy of probiotics. In some countries, such as the United States and Canada, probiotics are considered a food supplement and are not subject to the same regulatory oversight as drugs. However, other countries, such as Australia and the European Union, regulate probiotics as therapeutic goods and require manufacturers to provide evidence of safety and efficacy before being sold to the public. This regulatory oversight can help ensure that probiotics are safe and effective for human use[59].

7. Future directions and challenges

7.1. Future research on probiotics and urinary tract infections

Current research on probiotics and UTIs is rapidly expanding, and many promising avenues exist for future research[9]. One area of interest is the identification of optimal probiotic strains, dosages, and formulations for UTI prevention and treatment. To this end, researchers are investigating various strains of *Lactobacillus*, *Bifidobacterium*, and other bacteria to determine which ones are most effective in combating UTIs[31,32,52].

Another area of research is the development of probiotic formulations that can with stand harsh conditions in the urinary tract, such as acidic urine and bacterial competition. Researchers are exploring various technologies, such as microencapsulation, to enhance the survival and effectiveness of probiotics in the urinary tract[6-10].

In addition, researchers are investigating the mechanisms by which probiotics exert their beneficial effects on the urinary tract. This includes studying the interactions between probiotics and the host immune system, as well as the ways in which probiotics modulate the urinary microbiome[6-10].

7.2. Challenges and limitations of probiotics in urinary tract infections

There are several challenges and limitations to the use of probiotics for UTIs. One of the most significant challenges is the lack of standardization in probiotic products, with significant variability in the type and quantity of strains present in different products. This variability can make it difficult to compare results between studies or to determine optimal dosing[9].

Another challenge is the potential for probiotics to interact with other medications or conditions. For example, some strains of *Lactobacillus* have been associated with increased rates of fungal infections in immunocompromised individuals. Similarly, probiotics may interfere with the efficacy of antibiotics or other medications, leading to suboptimal treatment outcomes[31].

In addition, there is limited knowledge about the optimal strains and dosing of probiotics for UTI prevention and treatment, with some studies showing conflicting results. Furthermore, the effectiveness of probiotics may vary depending on the patient population, with some studies showing limited benefit in high-risk groups such as those with recurrent UTIs or catheter-associated infections[58].

7.3. Improvement in technology and administration of probiotics

While there have been some promising results with the use of probiotics for UTIs, there are also many challenges and limitations to their use. One potential area for improvement in probiotic technology is the development of more effective and targeted formulations[58].

A promising area of research is the use of engineered probiotics, which have been genetically modified to enhance their efficacy and targeting. For example, a study has indicated that the use of engineered *Lactobacillus crispatus* strains expressing D-mannose-binding lectin could prevent uropathogenic *E. coli* (UPEC) from adhering to the bladder wall. This approach could potentially be used to create probiotics that are more effective at preventing UTIs by specifically targeting the pathogens responsible for these infections[60].

Another potential area for improvement is the development of probiotic delivery systems that can better survive the harsh conditions of the urinary tract[61]. For example, one study has indicated that a probiotic formulation of *Lactobacillus crispatus* in alginate-chitosan microcapsules could survive the acidic conditions of the stomach and colon, as well as the bactericidal effects of urine. This approach could potentially be used to develop probiotics that can reach the urinary tract and colonize the bladder[61].

In addition, there is a need for a better understanding of the mechanisms of action of probiotics in UTIs, and the development of more effective methods for selecting and characterizing probiotic strains[62]. For example, the use of high-throughput sequencing and metabolomics could help to identify the specific mechanisms by which probiotics prevent and treat UTIs, as well as the specific strains and metabolites that are most effective. This could help to improve the efficacy and safety of probiotics for UTIs, and pave the way for the development of more targeted and effective probiotic therapies[62].

8. Conclusion

It is clear from the literature that probiotics have the potential to be a safe and effective alternative or complementary therapy for preventing and treating recurrent UTIs.

The implications of probiotics in clinical practice and public health are significant. The use of probiotics in preventing and treating UTIs can potentially reduce the overuse of antibiotics, which has been a major factor in the development of antibiotic resistance. Additionally, probiotics can prevent the occurrence of UTIs in vulnerable populations, such as women and the elderly. The use of probiotics can also potentially improve the quality of life for individuals with recurrent UTIs.

Future research on probiotics and UTIs should focus on identifying optimal strains, dosages, and delivery methods. Additional clinical trials are needed to evaluate the safety and efficacy of probiotics in different populations and to identify potential interactions with other medications. Studies are also needed to explore the use of probiotics in combination with antibiotics and to evaluate the long-term effects of probiotic use.

In conclusion, the use of probiotics in prevention and treatment of UTIs represents a promising area of research and clinical practice. While there are challenges and limitations to their use, the potential benefits are significant. Continued research and development of probiotic technology and administration can potentially improve the safety and efficacy of probiotics in prevention and treatment of recurrent UTIs. Overall, the potential of probiotics to combat UTIs is a promising avenue for improving public health and reducing the burden of antibiotic resistance.

Declarations

Competing interests

The authors declare that they have no conflict of interest.

Authors' contribution

All authors were involved in data collection, design of the article, interpretation of results, review, and manuscript preparation.

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The authors checked for plagiarism and consented to the publishing of the article. The authors have also checked the article for data fabrication, double publication, and redundancy.

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