

Probiotics as a Promising Strategy for Preventing Urinary Tract Infections: Mechanisms, Efficacy, and Clinical Evidence

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ABSTRACT

Urinary tract infections (UTIs) remain one of the most prevalent bacterial infections globally, with *Escherichia coli* accounting for most cases and women disproportionately affected due to anatomical and hormonal factors. Recurrent UTIs, which occur in up to 25% of initially affected women, continue to impose a substantial clinical burden despite the widespread use of antibiotics. However, increasing antimicrobial resistance has exposed the limitations of antibiotic-centric management and intensified interest in alternative strategies such as probiotics. Although strains including *Lactobacillus crispatus*, *L. rhamnosus*, and *L. reuteri* are frequently cited as promising candidates, the evidence supporting their efficacy remains heterogeneous and often strain-specific. Proposed mechanisms ranging from competitive exclusion and antimicrobial metabolite production to pH modulation and immune enhancement are biologically plausible, yet their consistency in vivo is not fully established. Clinical studies suggest that probiotics, particularly vaginally administered *L. crispatus*, may reduce recurrence by restoring urogenital microbial balance; however, variability in colonisation success, dosing regimens, and product standardisation complicates interpretation. Despite these limitations, probiotics offer theoretical advantages over antibiotics, including reduced adverse effects and no contribution to resistance. Future progress will depend on refining strain selection, optimising delivery systems, and strengthening mechanistic and clinical evidence. Overall, probiotics represent a potentially valuable adjunct or alternative for UTI prevention, but their widespread adoption requires more rigorous, standardised, and mechanistically informed evaluation.

Keywords: Probiotics, Urinary tract infections (UTIs), Lactobacillus, Microbiota, Antibiotic resistance, Urobiome.

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INTRODUCTION

Urinary tract infections (UTIs) remain among the most prevalent bacterial infections globally and continue to impose a substantial clinical and economic burden despite decades of research and therapeutic refinement.¹ Although UTIs are traditionally described as resulting from the ascension of intestinal bacteria into the urinary tract, this simplified model does not fully capture the complexity of host-microbe interactions or the variability in disease susceptibility.² The infection can involve any segment of the urinary system, yet the lower tract is disproportionately affected, reflecting both microbial dynamics and host anatomical factors. Whilst *Escherichia coli* remains the dominant uropathogen, the

involvement of *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Staphylococcus saprophyticus* underscores the polymicrobial and context-dependent nature of UTI pathogenesis.³

The disproportionate burden of UTIs in women is well recognised, but the underlying mechanisms, ranging from anatomical predisposition to hormonal modulation of the urogenital microbiota are still incompletely understood. Notably, up to 25% of women experience recurrence following an initial episode, highlighting persistent gaps in preventive strategies.⁴ Although antibiotic prophylaxis can reduce recurrence by as much as 85%,⁵ its long-term utility is increasingly undermined by escalating antimicrobial resistance. The emergence of resistant strains, driven by both clinical overuse and ecological disruption of commensal microbiota, has complicated treatment algorithms and reduced the reliability of standard therapies.^{6,7} These limitations have catalysed interest in non-antibiotic interventions, with probiotics frequently positioned as a biologically plausible alternative or adjunct.⁸



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Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts,⁹ have gained traction due to their potential to modulate microbial communities and influence mucosal immunity.¹⁰ However, the evidence supporting their role in UTI prevention is nuanced. While strains such as *Lactobacillus crispatus* have demonstrated promising reductions in recurrence, particularly when used vaginally or in combination with antibiotics,¹¹ outcomes remain highly strain-specific and dependent on successful colonisation. Furthermore, the assumption that probiotics uniformly restore microbial balance or inhibit uropathogen colonisation oversimplifies the complex ecological and immunological processes involved.¹²

This review critically evaluates the mechanistic rationale, clinical evidence, and translational challenges associated with probiotic-based UTI prevention. By interrogating both the strengths and limitations of current research, we aim to clarify the potential role of probiotics as adjuncts or alternatives to antibiotics, identify gaps that hinder clinical adoption, and outline future directions necessary to advance probiotic strategies within the broader context of antimicrobial resistance and urogenital health.

The Growing Challenge of Antimicrobial Resistance in UTI Management

Antimicrobial resistance (AMR) has emerged as one of the most formidable obstacles in contemporary UTI management, fundamentally undermining the reliability of conventional therapeutic strategies.¹³ Although the link between antibiotic misuse and resistance is well established, the persistence and acceleration of resistance patterns suggest that current stewardship efforts remain insufficient. The combined effects of inappropriate prescribing, incomplete treatment courses, and the efficient horizontal transfer of resistance genes have facilitated the rapid dissemination of multidrug-resistant uropathogens across diverse clinical settings.¹⁴ This trend is particularly concerning for UTIs, where *E. coli*, the predominant pathogen, has increasingly acquired resistance to multiple frontline antibiotics, thereby diminishing the effectiveness of standard empirical regimens.¹⁵

The growing prevalence of resistant UTIs has, paradoxically, intensified reliance on broad-spectrum antibiotics, despite their well-documented drawbacks. Whilst these agents may offer short-term therapeutic benefit, their use often exacerbates the very resistance pressures they are intended to overcome and exposes patients to significant adverse effects.¹⁶ Moreover, broad-spectrum therapy indiscriminately disrupts the gut microbiota, a disruption that not only contributes to dysbiosis but also heightens susceptibility to subsequent infections, creating a self-perpetuating cycle of antimicrobial exposure and microbial imbalance.¹⁷

Clinically, antibiotic-resistant UTIs are associated with higher rates of treatment failure, prolonged hospitalisation, and increased healthcare costs, reflecting both the direct burden of resistant infections and the indirect consequences of limited therapeutic options.¹⁸ In cases where resistance severely restricts available treatments, clinicians are often forced to resort to combination regimens, escalated dosing, or last-line antibiotics. These approaches carry substantial toxicity risks and may further accelerate resistance development, highlighting the fragility of current treatment paradigms.¹⁹ These challenges highlight the urgent need for alternative or adjunctive strategies capable of reducing antibiotic dependence and mitigating the escalating threat of AMR in UTI management.

Insights into the Urinary Microbiome: Composition and Function

The concept of a urinary microbiome or urobiome has fundamentally reshaped long-standing assumptions about urinary tract sterility, but the understanding of this microbial community remains incomplete and methodologically constrained.²⁰ For decades, urine was presumed sterile, a belief rooted more in the limitations of culture-based diagnostics than in biological reality.²¹ The advent of high-throughput sequencing technologies has overturned this paradigm by revealing a diverse, low-biomass microbial ecosystem within the urinary tract.²² However, despite these technological advances, the field is still in an early developmental stage. Current datasets are limited by small cohort sizes, inconsistent sampling methods, and a lack of representation from clinically relevant subgroups, including individuals with systemic diseases or recurrent UTIs.²³ As a result, the true diversity, stability, and functional significance of the urinary microbiota remain only partially characterised.

Compared with other microbial niches such as the gut, the urinary microbiota is markedly less abundant and less diverse, with typical bacterial loads in women ranging from 10^4 to 10^5 CFU/ml, several orders of magnitude lower than the gut microbiome.²⁴ This low-biomass environment complicates both detection and interpretation, increasing susceptibility to contamination and methodological artefacts. Nonetheless, emerging evidence indicates that the urobiome exhibits structured variation influenced by gender, race, and geography. Firmicutes dominate in both sexes, though with notable quantitative differences, followed by Actinobacteria, Bacteroidetes, and Proteobacteria.²⁵ Gender-specific patterns further highlight the biological relevance of this community: *Corynebacterium* and *Streptococcus* are more prevalent in men, whereas *Lactobacillus* predominates in women, reflecting hormonal and anatomical influences on microbial composition.²⁶ However, these observations are largely descriptive, and the extent to which such differences translate into functional or clinical consequences remains insufficiently explored.

Functionally, the urinary microbiota appears to contribute to mucosal homeostasis, but mechanistic insights are still emerging. Beneficial genera such as *Lactobacillus* and *Streptococcus* possess adaptations that facilitate colonisation, including type 1 fimbriae for urothelial adhesion and glycosaminoglycan-degrading enzymes that enhance nutrient acquisition.²⁷ These traits suggest an active ecological role rather than passive presence. However, the degree to which these mechanisms operate in vivo and how they interact with host immunity, urine chemistry, and pathogen dynamics remains poorly defined. Environmental factors such as pH, oxygen tension, and nutrient availability undoubtedly shape microbial behaviour, yet their specific contributions to urobiome stability and resilience are not well quantified.²⁸

Current evidence supports the existence of a structured urinary microbiome with potential relevance to urinary tract health, but substantial gaps persist. A more nuanced understanding of its composition, functional capacity, and interactions with host physiology is essential before the urobiome can be fully integrated into diagnostic or therapeutic frameworks.

The Role of Beneficial Bacteria in Urinary Tract Health

The urinary tract plays a central role in maintaining systemic homeostasis through the elimination of metabolic waste, but its microbial ecology has only recently been recognised as a contributor to urogenital health.²⁹ Although a balanced urinary microbiota is frequently described as essential for maintaining pH stability, epithelial integrity, and immune readiness, much of this understanding is extrapolated from higher-biomass niches such as the gut and vagina. Consequently, the specific contributions of urinary commensals remain less clearly defined than commonly assumed.

Beneficial genera, including *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Staphylococcus*, are often cited as key components of a healthy urinary ecosystem, but their roles are supported by uneven and sometimes indirect evidence.³⁰ For instance, *Lactobacillus* is widely regarded as protective due to its acidifying and antimicrobial properties, but its prevalence and functional dominance vary substantially across individuals and demographic groups. Similarly, the presence of *Bifidobacterium* and *Streptococcus* in the urinary tract is documented, but their mechanistic contributions to pathogen suppression or immune modulation remain poorly characterised. Even *Staphylococcus* species, typically associated with pathogenicity, may include commensal strains whose ecological roles are not fully understood.

Overall, whilst the concept of “beneficial bacteria” in the urinary tract is biologically plausible and supported by emerging evidence, the field still lacks comprehensive functional studies capable of distinguishing correlation from causation. A more rigorous understanding of how these taxa contribute to urinary tract resilience and how their disruption predisposes individuals to

infection is essential for advancing microbiome-based preventive strategies.

Lactobacillus: A Key Guardian of Urinary Tract Health

Lactobacillus species are the most abundant beneficial bacteria in the female urinary microbiota in maintaining a healthy urinary tract.³¹ These bacteria produce lactic acid, which lowers the pH of the urine, creating an acidic environment that is hostile to uropathogens such as *Escherichia coli*, the leading cause of UTIs.³² Additionally, *Lactobacillus* species secrete bacteriocins and other antimicrobial compounds that inhibit the adhesion and proliferation of harmful bacteria.

Lactobacillus species also contribute to urinary tract health through biofilm formation. These biofilms act as physical barriers on the epithelial lining of the urinary tract, preventing pathogenic bacteria from adhering to and colonising the area.³³ Furthermore, *Lactobacillus* stimulates the production of immunoglobulins and other immune responses, enhancing the body's ability to combat infections.³⁴ However, not all *Lactobacillus* species are associated with a healthy microbiota. For instance, whilst *Lactobacillus crispatus* is linked to a state of health, other species, such as *Lactobacillus gasseri*, have been associated with pathological conditions like urgency urinary incontinence (UUI).³⁵ A reduction in *Lactobacillus* abundance has been correlated with an increased risk of uropathogen colonisation and subsequent infections.³⁶

Maintaining Microbial Balance in the Urinary Tract

The maintenance of a balanced urinary microbiota is widely regarded as essential for urogenital health, but the mechanisms governing this balance and the factors that disrupt it remain incompletely understood. Dysbiosis, broadly defined as a disturbance in the composition or function of the microbial community, is frequently attributed to antibiotic exposure, hygiene practices, and hormonal fluctuations, but the relative contribution of each factor is still debated.³⁷ Antibiotics, although indispensable for treating acute infections, exert broad and often indiscriminate effects on microbial communities. Their capacity to eliminate both pathogenic and beneficial bacteria can precipitate substantial shifts in microbial diversity, weakening colonisation resistance and creating ecological niches that favour the expansion of opportunistic or antibiotic-resistant organisms.³⁸ This unintended consequence highlights a paradox in UTI management that the very agents used to treat infection may predispose individuals to future episodes by destabilising the urinary and adjacent microbiota.³⁹

Hormonal influences add an additional layer of complexity. Fluctuations associated with pregnancy, menopause, and the menstrual cycle can alter the physicochemical environment of the urinary tract, with downstream effects on microbial composition.⁴⁰ For example, estrogen deficiency during

menopause is strongly associated with reductions in *Lactobacillus* abundance, a shift that may facilitate pathogen overgrowth and increase UTI susceptibility.⁴¹ Similarly, hormonal changes during pregnancy and across the menstrual cycle can reshape both the vaginal and urinary microbiota, although the directionality and clinical significance of these changes are not fully resolved.⁴² Despite these associations, mechanistic studies linking hormonal variation to specific microbial or immunological outcomes remain limited, and much of the current understanding is extrapolated from vaginal rather than urinary microbiome research.

Overall, whilst dysbiosis is clearly linked to increased UTI risk, the pathways through which microbial imbalance arises and the extent to which it can be predictably corrected remain active areas of investigation. A more precise characterisation of the drivers and consequences of urinary microbiota disruption is essential for informing targeted, microbiome-based preventive strategies.

Dysbiosis and Increased Susceptibility to UTIs

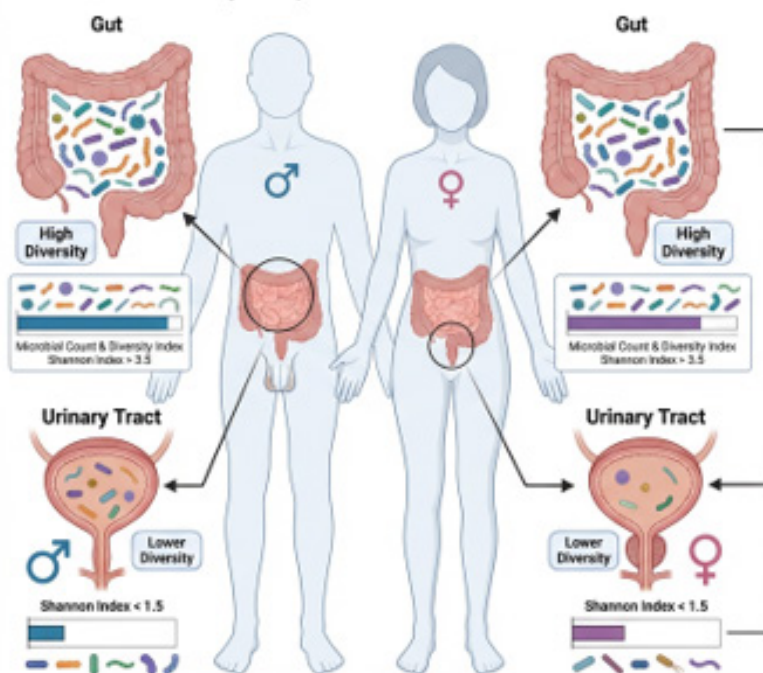
Dysbiosis of the urinary microbiota is strongly associated with heightened susceptibility to UTIs, yet the causal pathways linking microbial imbalance to infection risk remain only partially understood. A healthy urinary microbiota, typically enriched with protective taxa such as *Lactobacillus*, is thought to inhibit

uropathogen colonisation through multiple mechanisms, but much of this evidence is correlative rather than mechanistically resolved.⁴³ Declines in *Lactobacillus* abundance are frequently interpreted as a loss of protective capacity, particularly given the associated reduction in lactic acid and hydrogen peroxide production, both of which contribute to an acidic and antimicrobial urinary environment. However, the extent to which these metabolites exert sustained *in vivo* effects remains uncertain, especially in the context of urine flow and dilution.⁴⁴

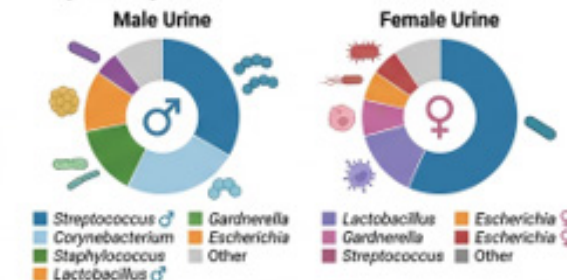
Microbial imbalance may also compromise mucosal immunity, with dysbiosis linked to reduced production of antimicrobial peptides and immunoglobulins that normally help neutralise invading bacteria.⁴⁵ However, the directionality of this relationship—whether dysbiosis weakens immunity or impaired immunity drives dysbiosis—has not been fully established. Inflammatory responses triggered by microbial disruption may further exacerbate vulnerability, creating a permissive environment for pathogen ascension and persistence.⁴⁶ Additionally, the loss of beneficial bacteria may destabilise protective biofilm structures on the uroepithelium, increasing epithelial exposure to pathogen adhesion and invasion.⁴⁷ Despite these proposed mechanisms, direct evidence demonstrating stable, functional biofilms formed by commensal species *in vivo* remains limited.

Urinary Microbiome Composition and Its Role in Maintaining Urinary Tract Health

A. Microbial Diversity Comparison



B. Key Urinary Microbial Taxa



C. Role in Urinary Tract Health

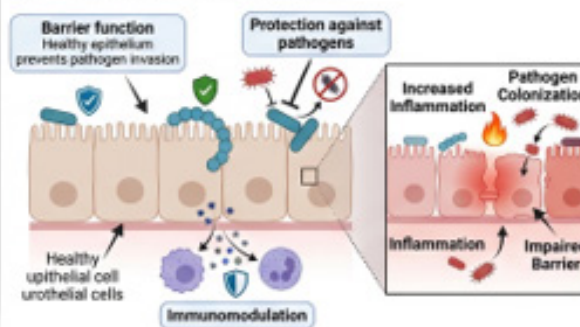


Figure 1: Schematic overview illustrating sex-specific differences in urinary microbiome diversity, dominant microbial taxa, and their functional contributions to urinary tract health. (a) Comparison of gut and urinary microbiome diversity in males and females, highlighting the lower microbial diversity characteristic of the urinary tract. (b) Representative composition of male and female urinary microbiota, showing genus-level differences including *Lactobacillus*, *Gardnerella*, *Streptococcus*, *Corynebacterium*, *Escherichia*, and *Staphylococcus*. (c) Functional roles of the urinary microbiome in maintaining epithelial barrier integrity, protecting against pathogen colonization, and modulating local immune responses, with impaired microbial balance associated with inflammation and increased susceptibility to infection.

Table 1: Comparative Summary of Oral and Vaginal Probiotic Delivery Routes for UTI Prevention.

Parameter	Oral Administration	Vaginal Administration	References
Primary Target Site	Gut microbiota → indirect modulation of urogenital microbiota.	Vaginal microbiota (direct local action).	82
Delivery Forms	Capsules, tablets, powders, liquids.	Suppositories, gels, vaginal capsules.	83
Mechanistic Pathway	• Survives GI tract → colonizes gut • Influences urinary/vaginal microbiota via gut-urinary axis • Some strains exert systemic immune effects.	• Direct colonization of vaginal epithelium • Restores Lactobacillus dominance • Rapid inhibition of uropathogens (e.g., <i>E. coli</i>).	84
Onset of Action	Slower (systemic route).	Faster (localized delivery).	85
Key Advantages	• Convenient daily use • Systemic health benefits • Compatible with synbiotics.	• Highly targeted • Rapid microbiota restoration • Strong efficacy for vaginal dysbiosis-linked UTIs.	86
Key Limitations	• Low survival through GI tract • Delayed therapeutic effect.	• Less convenient • Only applicable to women.	87
Clinical Evidence	<i>L. rhamnosus</i> GR-1 + <i>L. reuteri</i> RC-14 reduce UTI recurrence in women.	<i>L. crispatus</i> CTV-05 reduces recurrence by ~50% in premenopausal women.	88
Ideal Use Case	General female populations; individuals seeking systemic benefits.	Women with recurrent UTIs linked to vaginal dysbiosis.	89
Technological Enhancements	Microencapsulation improves GI survival.	Engineered strains enhance anti-adhesion activity.	90

These changes illustrate how dysbiosis may facilitate both initial infection and recurrence, but they also highlight the complexity of host-microbe interactions within the urinary tract. Whilst maintaining a balanced urinary microbiota is clearly associated with reduced UTI risk, the mechanistic underpinnings of this relationship require further clarification before dysbiosis can be reliably targeted in clinical interventions.

Addressing Dysbiosis through Probiotics

Probiotics are increasingly promoted as a strategy to restore microbial balance and reduce UTI risk, however, the evidence supporting their efficacy remains variable and often strain-dependent. The rationale for their use is grounded in the assumption that reintroducing beneficial bacteria can reconstitute key protective functions of the urinary microbiota, including lactic acid production, biofilm formation, and immune modulation but the extent to which these mechanisms operate reliably *in vivo* is still under investigation.⁴⁸ Whilst these proposed functions are biologically plausible, many studies rely on indirect markers of microbial restoration rather than direct demonstration of functional recovery within the urinary tract.

Probiotics are also positioned as a countermeasure to antibiotic-induced dysbiosis, with the potential to mitigate microbiota disruption and limit the emergence of resistant strains through competitive exclusion of uropathogens.⁴⁹ However, the degree to which probiotics can meaningfully reverse antibiotic-associated microbial shifts remains uncertain, particularly given the transient colonisation observed with

many strains and the variability in host receptivity. Moreover, the assumption that probiotics uniformly promote competitive exclusion oversimplifies the complex ecological interactions that govern microbial community structure.

Despite these limitations, ongoing research into strain optimisation, dosing strategies, and delivery systems continues to refine the therapeutic potential of probiotics. Advances in formulation and targeted delivery may enhance colonisation efficiency and mechanistic consistency, addressing some of the shortcomings observed in earlier studies. As such, probiotics represent a promising but still evolving adjunct or alternative to conventional antibiotic therapies. Their successful integration into UTI prevention frameworks will depend on more rigorous mechanistic validation, standardised clinical protocols, and clearer identification of patient populations most likely to benefit.

Probiotics: Mechanisms of Action in UTI Prevention

The proposed mechanisms through which probiotics prevent UTIs are diverse and conceptually compelling, but the strength of empirical support varies considerably across studies. Probiotics are often described as acting through direct antagonism of uropathogens, modulation of host immune responses, and restoration of microbial balance within the urinary and vaginal microbiota.⁵⁰ Whilst these mechanisms provide a biologically plausible framework, much of the evidence remains fragmented, strain-specific, or derived from experimental systems that do not fully replicate the complexity of the human urogenital environment.

Direct interactions with uropathogens, such as competitive exclusion, interference with adhesion, and secretion of antimicrobial metabolites are frequently cited as key protective pathways. However, the consistency and durability of these effects *in vivo* remain uncertain, particularly given the transient colonisation observed with many probiotic strains. Similarly, claims of immune modulation, including enhanced mucosal immunity and increased production of antimicrobial peptides, are supported primarily by preclinical data, leaving important gaps regarding their clinical relevance and reproducibility in human populations.

The restoration of microbial balance is often positioned as a central mechanism; however, this concept assumes a level of ecological stability and host receptivity that may not be universally present. The urinary and vaginal microbiota are dynamic systems influenced by hormonal, behavioural, and environmental factors, and the ability of probiotics to meaningfully reshape these communities remains variable. Moreover, the extent to which microbiota restoration directly translates into reduced UTI risk has not been conclusively demonstrated.

Overall, whilst probiotics exhibit multiple mechanistic pathways that could theoretically reduce UTI incidence and mitigate antibiotic resistance, the current evidence base is still evolving. A more rigorous, mechanistically grounded understanding of these

pathways is essential for determining which probiotic strains, delivery routes, and dosing strategies are most likely to yield clinically meaningful benefits.

Competitive Exclusion: Blocking Pathogen Adherence

Competitive exclusion is frequently cited as a central mechanism through which probiotics may prevent UTIs, yet the robustness and consistency of this mechanism *in vivo* remain subjects of ongoing debate. The concept that beneficial bacteria outcompete uropathogens for adhesion sites and nutrients is biologically plausible and supported by *in vitro* observations, particularly against *E. coli*, the predominant uropathogen.⁵¹ *Lactobacillus* species are often highlighted for their ability to bind uroepithelial receptors, thereby occupying niches that would otherwise be exploited by pathogens. However, the extent to which these interactions occur reliably within the dynamic urinary environment is not fully established, and evidence of sustained epithelial colonisation remains limited.⁵²

Probiotics are also described as possessing strong adhesion properties mediated by surface proteins and exopolysaccharides, which may facilitate the formation of protective biofilms. These biofilms are proposed to stabilise the microbial community and create a physical barrier that restricts pathogen access to the

Probiotic Actions in UTI Prevention

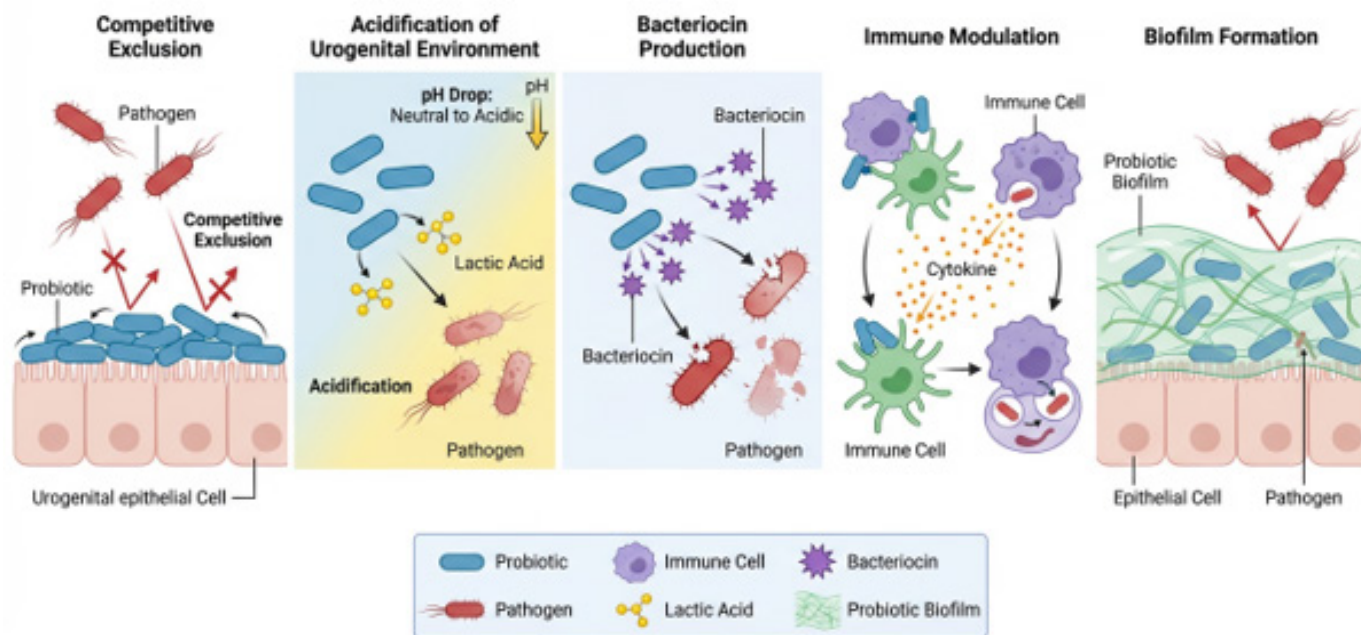


Figure 2: Probiotic Mechanisms Involved in the Prevention of Urinary Tract Infections. Illustration summarizing the five principal biological mechanisms through which probiotics contribute to UTI prevention: (1) Competitive exclusion, where probiotics occupy epithelial binding sites and block pathogen adhesion; (2) Acidification of the urogenital environment through lactic acid production, creating a low pH milieu unfavourable to uropathogens; (3) Bacteriocin production, involving secretion of antimicrobial peptides that inhibit or kill pathogenic bacteria; (4) Immune modulation, whereby probiotics stimulate host immune cells and enhance cytokine mediated defense responses; and (5) Biofilm formation, in which probiotics establish a protective biofilm on epithelial surfaces that acts as a barrier against pathogen invasion.

Comparative Analysis of Oral and Vaginal Probiotic Delivery for UTI Prevention

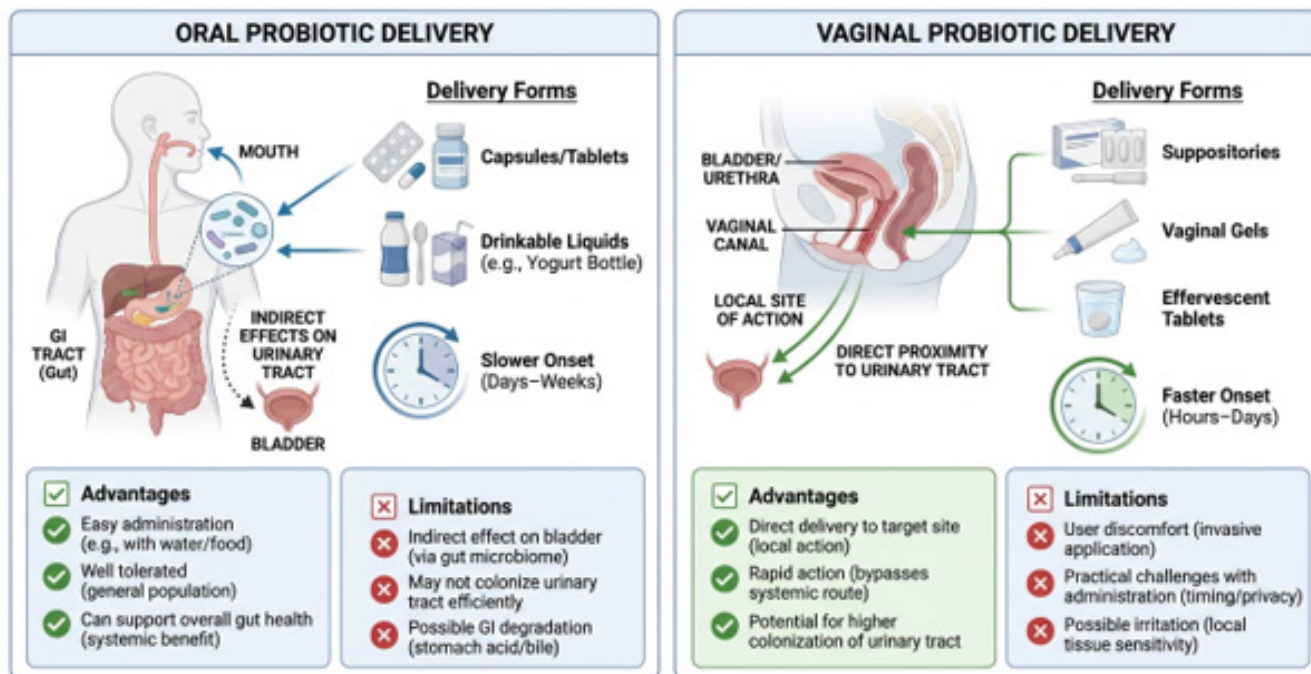


Figure 3: Illustration comparing the characteristics, pathways, and clinical implications of oral versus vaginal probiotic administration for urinary tract infection prevention. The oral route involves ingestion of capsules, tablets, or liquid formulations that transit the gastrointestinal tract and exert indirect effects on the urinary system, with a slower onset of action due to systemic modulation. Advantages include ease of use, broad tolerability, and additional gut-health benefits, while limitations include reduced urinary tract colonization and potential degradation by gastric acid and bile. In contrast, vaginal delivery via suppositories, gels, or effervescent tablets provides direct, localized action with faster onset, enhanced colonization of the urogenital tract, and targeted restoration of vaginal microbiota. Limitations include user discomfort, practical challenges with application, and potential local irritation.

uroepithelium.⁵³ However, much of the supporting evidence derives from laboratory models that do not replicate the shear forces, nutrient fluctuations, and host immune interactions characteristic of the urinary tract. Demonstrations of durable, functional probiotic biofilms *in vivo* are sparse, raising questions about the translational relevance of these findings.

Whilst competitive exclusion remains an attractive mechanistic explanation, its effectiveness likely varies by strain, host physiology, and delivery route. The assumption that probiotics can reliably establish a “robust presence” in the urinary tract may overstate current evidence, particularly given the transient colonisation observed in many clinical studies. A more nuanced understanding of the ecological and host-dependent factors governing probiotic adhesion is essential before competitive exclusion can be considered a consistently effective mechanism for UTI prevention.

Antimicrobial Activity: Neutralizing Uropathogens

Probiotics are widely described as exerting antimicrobial effects through the production of compounds such as bacteriocins, hydrogen peroxide, and lactic acid, but the strength and consistency of these effects *in vivo* remain incompletely characterised.⁵⁴ Whilst these metabolites can inhibit uropathogen growth

under controlled laboratory conditions, their concentrations and stability within the urinary tract, an environment marked by continuous dilution, variable pH, and rapid turnover are far less certain. The commonly cited role of lactic acid in lowering urinary pH, for example, may overstate its physiological impact, given that urine acidity is influenced by host metabolism and diet as much as by microbial activity.

In addition to acidification, some probiotic strains are reported to secrete anti-adhesion metabolites capable of interfering with pathogen attachment mechanisms, including fimbriae and pili used by *E. coli* and other Uropathogens.⁵⁵ Although these findings provide a compelling mechanistic rationale, most supporting evidence derives from *in vitro* assays that do not fully replicate the complexity of host-pathogen interactions in the urinary tract. The extent to which these anti-adhesion effects translate into meaningful clinical protection therefore remains uncertain.

Whilst antimicrobial metabolite production represents a plausible pathway through which probiotics may neutralise uropathogens, the current evidence base is limited by experimental constraints and a lack of robust *in vivo* validation. More rigorous studies are needed to determine whether these mechanisms operate at physiologically relevant levels and contribute substantively to UTI prevention.

Immune System Modulation: Enhancing Host Defenses

Immune modulation is frequently proposed as a key mechanism through which probiotics may enhance host defence against UTIs. Again, much of the supporting evidence remains preliminary and derived from experimental systems rather than robust clinical studies. Probiotics are reported to influence both innate and adaptive immune responses, potentially strengthening mucosal defences against Uropathogens.⁵⁶ For example, certain strains can stimulate the production of antimicrobial peptides such as defensins and cathelicidins, which disrupt bacterial membranes. They may also enhance the activity of phagocytic cells, including macrophages and neutrophils, thereby promoting more efficient clearance of invading pathogens. However, the extent to which these immunomodulatory effects occur at physiologically meaningful levels within the urinary tract remains uncertain.

Interactions between probiotics and toll-like receptors (TLRs) on uroepithelial cells are also proposed to trigger cytokine release and immune cell recruitment, theoretically bolstering early responses to infection. Similarly, increased secretion of secretory immunoglobulin A (sIgA) has been suggested as a mechanism by which probiotics could neutralise pathogens and prevent epithelial adhesion.⁵⁷ However, most evidence for these pathways originates from *in vitro* or animal models, and direct

confirmation in human urinary tissues is limited. Moreover, the immune effects of probiotics are highly strain-specific, raising questions about the generalisability of these findings.

Probiotics are also thought to modulate T-cell responses, potentially reducing excessive inflammation that can damage uroepithelial tissues and facilitate infection.⁵⁸ Whilst this anti-inflammatory potential is appealing, the balance between protective and suppressive immune modulation is delicate and insufficiently characterised in the context of UTIs. Without clearer mechanistic evidence, it remains difficult to determine whether these immunological effects contribute meaningfully to clinical outcomes.

Overall, although immune modulation represents a plausible mechanism of probiotic action, the current evidence base is limited by reliance on preclinical models and a lack of direct *in vivo* validation. More rigorous human studies are needed to clarify the extent, consistency, and clinical relevance of probiotic-mediated immune enhancement in UTI prevention.

Restoring Microbial Balance: A Holistic Approach to UTI Prevention

Restoring microbial balance across the gut, vaginal, and urinary microbiota is frequently presented as a holistic mechanism

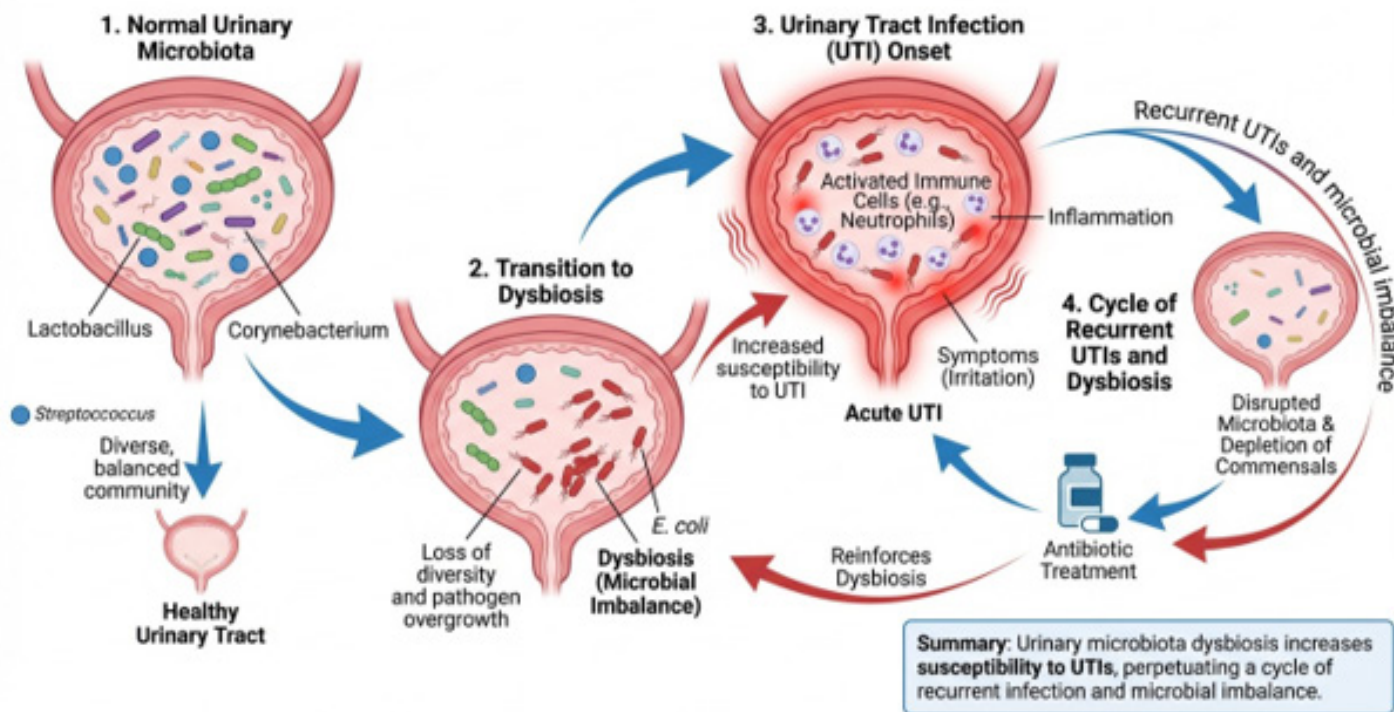


Figure 4: Dysbiosis of the Urinary Microbiota and Its Contribution to Recurrent Urinary Tract Infections. Schematic representation illustrating the progression from a healthy urinary microbiota to dysbiosis and recurrent urinary tract infections (UTIs). (a) Normal urinary microbiota, characterised by a balanced community of commensal taxa such as *Lactobacillus*, *Corynebacterium*, and *Streptococcus*, supports epithelial integrity and pathogen resistance. (b) Transition to dysbiosis, marked by reduced microbial diversity and overgrowth of uropathogens including *Escherichia coli*. (c) Acute UTI onset, showing epithelial inflammation and immune activation in response to pathogen invasion. (d) Cycle of recurrent UTIs, where antibiotic exposure and persistent microbial imbalance further disrupt commensal populations, perpetuating susceptibility to repeated infections. The summary highlights how dysbiosis destabilizes urinary tract homeostasis and reinforces the recurrence cycle.

Table 2: Comparison of Conventional Probiotics, Engineered Probiotics, and Advanced Delivery Technologies for UTI Prevention.

Category	Key Features	Mechanism of Action	Advantages	Limitations	References
Conventional Probiotics	Naturally occurring strains such as <i>L. crispatus</i> , <i>L. rhamnosus</i> GR-1, <i>L. reuteri</i> RC-14.	• Restore Lactobacillus-dominant microbiota • Produce lactic acid, bacteriocins • Compete with uropathogens for adhesion sites.	• Clinically validated • Safe and widely available • Effective for recurrent UTIs.	• Variable colonization • Sensitive to GI/vaginal conditions • Limited strain-specific targeting.	91
Engineered Probiotics	Genetically modified strains designed for enhanced anti-uropathogenic activity.	• Expression of anti-adhesive molecules (e.g., D-mannose-binding lectin) • Enhanced pathogen inhibition • Improved mucosal binding.	• Highly targeted action • Potential for personalized therapy • Strong anti-adhesion effects.	• Regulatory challenges • Safety validation required • Limited clinical trials.	92
Microencapsulation Technologies	Alginate-chitosan microgels and similar protective matrices.	• Protect probiotics from gastric acid, bile, and urinary stressors • Improve survival and delivery to target sites.	• Enhanced viability • Controlled release • Improved colonization efficiency.	• Manufacturing complexity • Cost considerations.	93
Synbiotic Formulations	Combination of probiotics + prebiotics	• Prebiotics enhance probiotic growth and activity • Promote stable colonization	• Synergistic effects • Improved microbiota modulation	• Prebiotic selection must match strain • GI tolerance varies	94
Targeted Vaginal Delivery Systems	Vaginal capsules, gels, bioadhesive formulations	• Direct delivery to vaginal epithelium • Rapid microbiota restoration	• Fast onset • High local concentration • Effective for dysbiosis-linked UTIs	• Limited to female populations • Requires adherence to application schedule	95

through which probiotics may reduce UTI risk. However, the evidence supporting this interconnected model remains uneven. The gut-vagina-urinary axis is biologically plausible, given the anatomical proximity and microbial exchange between these niches, but the precise pathways through which dysbiosis in one site influences susceptibility in another are still being elucidated.⁵⁹ Whilst disruptions in these microbial communities are associated with increased UTI risk, the causal relationships are complex and not fully defined.

Probiotics are proposed to counteract dysbiosis by reintroducing beneficial bacteria capable of re-establishing a stable microbial environment and reducing opportunities for pathogen colonization.⁶⁰ However, the extent to which orally or vaginally administered probiotics can reliably and durably reshape these communities remains uncertain. Colonisation success is highly strain-specific and often transient, raising questions about the long-term stability of probiotic-induced microbial changes.

In addition to their ecological effects, probiotics produce metabolites such as lactic acid, which may contribute to pathogen suppression by lowering urinary pH and creating a less favourable environment for Uropathogens.^{61,62} However, the physiological relevance of these pH-modulating effects *in vivo* is not fully established, particularly given the dynamic nature of urine production and flow. As such, the contribution of lactic acid to sustained pathogen inhibition may be more limited than commonly assumed.

Overall, whilst the concept of restoring microbial balance offers an appealing, systems-level framework for UTI prevention, current evidence remains largely associative and mechanistic validation is incomplete. Probiotics may indeed support microbial recovery and reduce dysbiosis-associated vulnerability, but their effectiveness depends on strain selection, host factors, and delivery strategies that are not yet optimised. A more rigorous understanding of how probiotics influence microbial networks

across the gut-vagina-urinary axis is essential before this holistic approach can be fully integrated into clinical practice.

DISCUSSION

Probiotics continue to attract interest as a potential strategy for UTI prevention, yet the evidence supporting their use requires careful interpretation. Although the urinary tract harbours a structured microbiome with demonstrable roles in mucosal integrity and immune regulation,⁶³ the functional significance of many detected taxa remains incompletely understood. As illustrated in Figure 1, the urinary microbiome is less diverse than the gut microbiome, but includes genera such as *Lactobacillus*, *Gardnerella*, *Streptococcus*, and *Corynebacterium*, which may contribute to epithelial barrier maintenance and pathogen exclusion.^{64,65} However, the stability of this community is highly sensitive to perturbations, including antibiotic exposure, hormonal fluctuations, and pathogen invasion, highlighting the fragility of urinary tract homeostasis and the potential value of interventions that support microbial resilience.⁶⁶

Figure 2 summarises the mechanistic pathways through which *Lactobacillus* species may counteract dysbiosis, including competitive exclusion, acidification, bacteriocin production, immune modulation, and interference with pathogenic biofilms.⁶⁷

Whilst these mechanisms provide a coherent biological rationale, their consistency *in vivo* remains variable, and many studies rely on surrogate markers rather than direct demonstration of functional effects within the urinary tract. The distinction between mechanistic plausibility and clinical reliability is therefore critical when evaluating probiotic efficacy.

The mode of probiotic administration further complicates interpretation. As shown in Figure 3, oral and vaginal delivery routes differ markedly in their mechanistic pathways and practical limitations. Oral probiotics offer convenience and may influence the gut-urinary axis, but their indirect action and susceptibility to gastrointestinal degradation can delay or diminish therapeutic impact.⁶⁸ Vaginal delivery provides more targeted exposure but raises challenges related to colonisation consistency and patient acceptability. Figure 4 reinforces the importance of microbial balance by depicting the progression from eubiosis to dysbiosis, acute infection, and recurrence.^{69,70} This cyclical pattern underscores the need for interventions that restore, rather than further disrupt, microbial ecology.

Recent biotechnological advances have expanded the scope of probiotic therapy beyond conventional strains. Figure 5 highlights innovations such as engineered probiotics expressing anti-adhesive molecules or enhanced antimicrobial peptides,⁷¹

Table 3: Core Mechanistic Pathways through Which Probiotics Prevent Urinary Tract Infections.

Mechanistic Pathway	Description	Functional Outcomes Relevant to UTI Prevention	Representative Strains / Technologies	References
Acidification of the Urogenital Environment	Production of lactic acid lowers vaginal pH, creating an inhospitable environment for uropathogens.	• Inhibits growth of <i>E. coli</i> and other uropathogens • Promotes <i>Lactobacillus</i>-dominant microbiota	<i>L. crispatus</i> , <i>L. jensenii</i>	96
Bacteriocin Production	Secretion of antimicrobial peptides that directly inhibit pathogenic bacteria.	• Suppresses pathogen colonization • Enhances competitive exclusion	<i>L. rhamnosus</i> GR-1, <i>L. reuteri</i> RC-14	97
Competitive Exclusion of Pathogens	Probiotics occupy adhesion sites on epithelial surfaces, preventing pathogen attachment.	• Blocks <i>E. coli</i> adherence to vaginal and urinary epithelium • Reduces risk of ascending infection	<i>L. crispatus</i> CTV-05; engineered strains expressing anti-adhesion molecules	98
Immune Modulation	Probiotics modulate local and systemic immune responses, enhancing host defense.	• Strengthens mucosal immunity • Reduces inflammation associated with recurrent UTIs	Oral <i>Lactobacillus</i> species	99
Biofilm Disruption	Some strains disrupt pathogenic biofilms or prevent their formation.	• Reduces persistence of uropathogens • Enhances clearance of recurrent infections	Select <i>Lactobacillus</i> strains; engineered variants	100
Enhanced Survival via Delivery Technologies	Microencapsulation and protective matrices improve probiotic viability.	• Increased delivery to target sites • Improved colonization and therapeutic consistency	Alginate-chitosan microgels	101

Advanced Probiotic Technologies for UTI Prevention

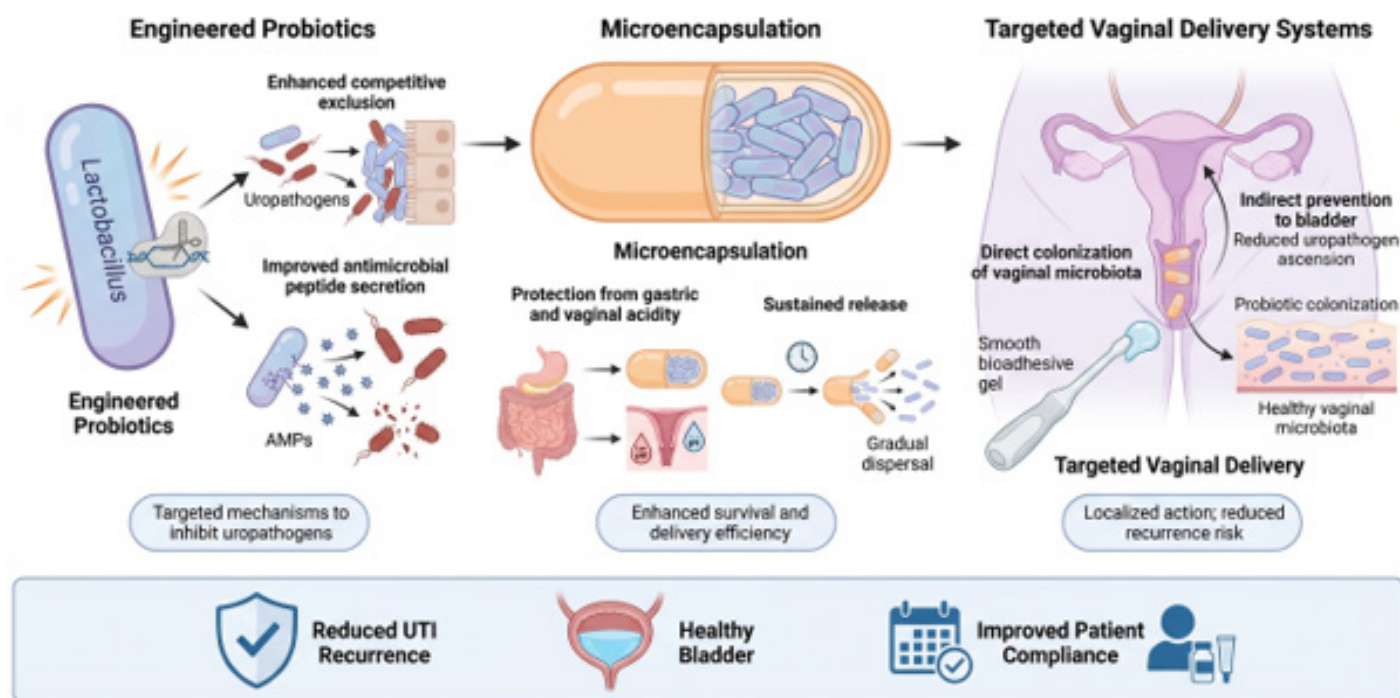


Figure 5: Advanced Probiotic Technologies for Enhancing UTI Prevention. Schematic overview of emerging probiotic-based strategies designed to improve efficacy, survival, and targeted delivery for urinary tract infection prevention. The figure highlights three key technological approaches: (a) Engineered probiotics, in which genetically modified *Lactobacillus* strains exhibit enhanced competitive exclusion and increased antimicrobial peptide secretion to inhibit uropathogens; (b) Microencapsulation systems, providing protective matrices that shield probiotics from gastric and vaginal acidity while enabling sustained release and improved delivery efficiency; and (c) Targeted vaginal delivery platforms, including bioadhesive gels that promote direct colonization of the vaginal microbiota, reduce uropathogen ascension, and support restoration of a healthy urogenital environment. Collectively, these innovations aim to reduce UTI recurrence, support bladder health, and improve patient adherence.

microencapsulation technologies that improve viability and sustained release,⁷² and targeted vaginal delivery systems, including bioadhesive gels that enhance colonisation efficiency and reduce pathogen ascension.⁷³ These developments aim to address long-standing limitations related to strain survival, mucosal adherence, and mechanistic consistency, signalling a shift toward more sophisticated, mechanism-driven probiotic strategies.

Tables 1 and 2 synthesise the comparative strengths and limitations of oral versus vaginal delivery and contrast conventional probiotics with engineered strains, microencapsulation platforms, synbiotics, and targeted delivery systems. Table 3 consolidates the mechanistic foundations of probiotic action, aligning these pathways with the biological processes disrupted during dysbiosis and recurrent infection. Collectively, these tables and figures illustrate both the promise and the complexity of probiotic-based interventions.

Despite encouraging findings, clinical evidence remains heterogeneous. Although several studies report reductions in UTI recurrence, particularly among women with recurrent infections; variability in strain selection, dosing regimens, delivery routes, and study design limits comparability across trials.^{74,75}

Strengthening the evidence base will require standardised clinical protocols, microbiome-guided patient stratification, and direct comparisons with antibiotic prophylaxis.^{76,77} Future research should prioritise personalised probiotic therapies informed by urinary and vaginal microbiome profiling, combination strategies integrating probiotics with non-antibiotic interventions such as D-mannose or immunomodulators, and long-term safety and efficacy assessments of engineered strains and advanced delivery systems.⁷⁸ Special populations, including postmenopausal women, pregnant individuals, and patients with neurogenic bladder also require dedicated evaluation to determine whether probiotic benefits are generalisable or context-specific.⁷⁹⁻⁸¹

In summary, the integrated evidence presented in this review demonstrates that probiotics represent a biologically plausible and increasingly sophisticated approach to UTI prevention. Their capacity to restore microbial balance, inhibit uropathogens, and modulate host immunity, combined with advances in delivery technologies positions them as a viable complement or alternative to antibiotic prophylaxis. However, realising their full potential will depend on continued innovation, rigorous mechanistic validation, and well-designed clinical trials capable of resolving current uncertainties and guiding evidence-based implementation.

CONCLUSION

Probiotics have emerged as a biologically plausible and increasingly sophisticated strategy for preventing recurrent urinary tract infections, supported by growing evidence that the urinary, vaginal, and gut microbiota play integral roles in maintaining urogenital health. Their capacity to restore microbial balance, inhibit uropathogen colonisation, and modulate host immune responses positions them as a compelling complement or, in selected cases, an alternative to antibiotic prophylaxis. However, the clinical effectiveness of probiotic interventions remains influenced by multiple factors, including strain specificity, dosing regimen, delivery route, and host-dependent microbial ecology. As highlighted in recent comparative analyses, the choice between oral and vaginal administration should be guided by individual clinical needs and the underlying drivers of dysbiosis, with oral delivery offering systemic modulation and convenience, and vaginal delivery providing more targeted action for localised microbial disruption.

Advances in biotechnology are accelerating the evolution of probiotic therapies beyond conventional formulations. Microencapsulation platforms that enhance viability and sustained release, along with engineered strains capable of expressing anti-adhesive or antimicrobial molecules, offer promising avenues for improving colonisation efficiency, mechanistic consistency, and therapeutic durability. These innovations address long-standing limitations associated with probiotic survival, mucosal adherence, and variability in clinical outcomes, and they hold the potential to significantly strengthen the role of probiotics in UTI prevention.

Realising this potential will require rigorous, standardised clinical trials, microbiome-guided patient stratification, and long-term safety assessments, particularly in populations with heightened vulnerability to recurrent UTIs. Integrating probiotics with other non-antibiotic strategies, such as D-mannose, immunomodulators, or targeted vaginal delivery systems may further enhance therapeutic outcomes. As the field advances, probiotics are poised to contribute meaningfully to a more sustainable, microbiome-informed approach to UTI management, reducing reliance on antibiotics and helping to mitigate the global challenge of antimicrobial resistance.

ABBREVIATIONS

AMR: Antimicrobial Resistance; **UTI:** Urinary Tract Infection; **UTIs:** Urinary Tract Infections; **UUI:** Urgency Urinary Incontinence; **GI:** Gastrointestinal; **TLRs:** Toll-Like Receptors; **slgA:** Secretory Immunoglobulin A; **CFU:** Colony Forming Units; **DNA:** Deoxyribonucleic Acid; **GR-1:** *Lactocaseibacillus rhamnosus* GR-1 strain; **RC-14:** *Limosilactobacillus reuteri* RC-14 strain; **CTV-05:** *Lactobacillus crispatus* CTV-05 strain.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization was carried out by T.A.N and O.O.O.; V.A. and I.E.C. transformed T.A.N's manuscript work into a structured manuscript. Methodology was developed by T.A.N. and O.O.O., with image software support provided by V.A. Validation was performed by T.A.N., V.A. and I.E.C. Formal analysis and investigation were conducted by T.A.N. Resources and data curation were provided by T.A.N and V.A. The original manuscript draft was written by T.A.N, with subsequent review and editing undertaken by T.A.N., V.A. and I.E.C. Visualization was completed by V.A. and I.E.C, while supervision was provided by V.A. and I.E.C. Project administration was managed by V.A. All authors have read and approved the final version of the manuscript.

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