Review

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Urinary Tract Microbiome Association with Diseases and Autoimmunity: Plausible Potential for Therapeutics and Accompanying Challenges

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Abstract: The urinary tract, once considered sterile, is now understood to host a diverse community of microorganisms known as the urinary microbiome. This microbiome, which is made up of bacteria, fungi, and viruses, is important for preserving urological health and has been linked to the pathogenesis of a number of urinary tract disorders. In this review, we offer a consolidated overview of the urinary tract bacterial population, including its composition, diversity, and factors influencing its dynamics. We explore its involvement in urinary tract infections, interstitial cystitis/bladder pain syndrome (IC/BPS), urinary stone formation, and other urological diseases, highlighting the importance of understanding its correlation with disease pathology for the development of therapeutic strategies. Additionally, we explore its role in autoimmune diseases of the urinary tract and the potential of leveraging the urinary microbiome for targeted interventions in the treatment of urinary tract infections. Longitudinal studies are emphasized for their ability to elucidate microbial dynamics, establish causality, and ensure consistency and reproducibility across research endeavors. These efforts underscore the necessity for continued research and multidisciplinary collaborations in this rapidly evolving field to advance our understanding and therapeutic strategies for urinary tract disorders.

Keywords: urinary tract; microbiome; culturing; metagenomic sequencing; urinary tract diseases; dysbiosis; probiotics

1. Introduction

The establishment of the Human Microbiome Project (HMP) in 2008 marked the beginning of a new chapter in our knowledge of the microbial populations that live inside of us. [1]. The population of bacteria that thrives in the urinary system, encompassing kidneys, ureters, bladder, and urethra, constitutes the urinary tract (UT) microbiome[2,3]. Although the urinary system was once thought to be sterile, advances in molecular biology techniques have shown that a wide variety of bacteria, fungi, and viruses may be present there [4]. The UT microbiome preserves the integrity of the associated epithelium, protect against infections and foster the appropriate operation of the immune system[5]. It maintains the urinary tract homeostasis through various mechanisms, including the regulation of pH levels, production of antimicrobial peptides, and competition for resources, which collectively help to establish and preserve a balanced urinary tract environment[6]. The human immune system and the epithelial cells lining the UT interact with the microbiota, which may impact the

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inflammatory and immunological responses[7]. Stimulation of host defense by modulating immune system can play crucial roles in defending against pathogens and maintaining tissue integrity.

The microbial composition of the urinary tract microbiota is influenced by various factors, including host genetics, anatomy, immune function, and external factors such as diet and antibiotic use[8]. The microbiota typically includes bacteria, but fungi and viruses may also be present in smaller quantities[9]. Roughly 90% of samples with no growth by normal urine culture contain live bacteria, according to studies using both 16S rRNA amplicon sequencing and advanced urine culture [10]. In healthy individuals, the urinary tract microbiota is often dominated by a few bacterial species, primarily from the genera Lactobacillus[11]. Numerous urological conditions, including UT infections, incontinence, bladder pain syndrome and urinary stone formation have been related to changes in the microbial community composition[12,13]. Several bacteria and fungi can cause UT infections, but the most frequent culprits are uropathogenic bacteria *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabili,s Staphylococcus saprophyticus, Enterococcus faecalis*, *Proteus mirabilis* [14] and fungus *Candida sp*.[15,16]. The urinary tract microbiota is dynamic and can change in response to various factors, such as hormonal fluctuations, sexual activity, urinary tract infections, and antibiotic treatment[17,18]. These changes can affect the balance of beneficial and potentially pathogenic microorganisms. Overall, urobiota contributes to the maintenance of the bladder homeostasis[19] and dysbiosis in it leads to health issues[20]. The diversity of the UT microbiota communities and their impact on health, namely the distinction between eubiosis and dysbiosis, are the subject of ongoing research. The present goal of scientific study on the UT microbiota is to comprehend the potential function that it may play in the development of UTIs as well as other medical conditions including cancer and other UIs [4]. Understanding the urinary tract microbiota has important clinical implications for the diagnosis and management of urinary tract infections and other urinary tract disorders[18,21]. For example, changes in the urinary microbiota may influence susceptibility to infections, treatment outcomes, and recurrence rates.

2. Methods to Study the Microbiome

While conventional urine culture methods primarily targeted aerobic microorganisms and pathogens like *Escherichia coli*, molecular techniques offer a more comprehensive view of the urinary microbiota[22,23]. Advent of cutting-edge molecular techniques have helped us get a better picture of the microbial population in the UT system. Urine microbiome can now be studied by two major methods; microbial culturing and metagenomic sequencing[24].

2.1. Microbial Culturing

To study UT microbiota, urine samples are usually tested for the presence of urinary pathogens using culture-dependent techniques. Standard urine culture, which includes plating urine onto agar plates containing 5% sheep blood agar as well as MacConkey agar plates and incubation aerobically at 35°C for 24 hours to produce quantitative colony counts, is the primary approach used to diagnose UTIs [25]. Nevertheless, the detection of bacteria in urine is severely limited by this approach, as the diagnostic criteria are ≥105. This traditional method for diagnosing urinary tract infections (UTIs), often misses low bacterial counts. Enhanced quantitative urine culture (EQUC) offers a more sensitive approach by utilizing larger urine volumes, multiple incubation durations, diverse culture media, varied incubation atmospheres (CO_2-enriched, aerobic, anaerobic, microaerobic)[26]. Compared to standard culture, EQUC can detect 88% of non-*E. coli* uropathogens and 67% of all uropathogens missed by standard culture[27]. However, it still has limitations and this can lead to misdiagnosis and inappropriate treatment.

2.2. Metagenomic Sequencing

The entire range of persistent microbial communities in the human UT and UGT is undetectable, even by EQUC[28]. With next generation sequencing (NGS) based metagenomic sequencing techniques, researchers have evaluated the entire microbial composition without bias. Currently, 16S

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rRNA amplicon sequencing and shotgun metagenomic sequencing are the two main methods of metagenomic sequencing [29]. 16S rRNA Amplicon Sequencing involves deep sequencing of amplicons encompassing variable regions of the 16S rRNA gene, enabling ecological structure assessment, community profiling, and sequence identification through subsequent bioinformatics analyses [30]. While this method offers sensitive detection of low-abundance microbial DNA with minimal host contamination, it suffers from inherent bias in primer binding, limiting its application to taxonomic analysis and relative abundance assessments [31,32]. Conversely, shotgun metagenomics sequences all DNA molecules present in a sample, providing an in-depth analysis of the entire sequence space. Despite its potential for detailed examination, it often encounters host contamination, necessitating sufficient sequencing depth to discern microbial populations accurately[33]. Strategies to enhance microbial DNA enrichment through refined sample preparation and DNA extraction methods are crucial for minimizing host contamination. The comprehensive analysis of the metagenome facilitates the determination of taxonomic composition, community structure, and functional attributes of the local microbiota's genetic potential. Nonetheless, 16S rRNA sequencing remains prevalent in human urine microbiome studies, primarily due to its utility in community taxonomic profiling[34].

3. Variability of UT Microbiome

Variability in the composition and diversity of the microbiome stems from a myriad of factors encompassing age, gender, diet, lifestyle, and overall health status[35]. Predominantly, bacterial infections of the UT afflict adults, with microbial analyses revealing distinct microbial profiles across age and gender cohorts[17,36]. In individuals around 18 years old, prevalent taxa include *Lactobacillus, Corynebacterium, Escherichia*, and *Streptococcus sp.*, whereas 28-year-old males exhibited *Lactobacillus, Sneathia, Veillonella, Corynebacterium,* and *Prevotella*. Females aged 27–67 years showcased a microbial landscape dominated by *Lactobacillus, Prevotella, Gardnerella, Peptoniphilus*, and *Dialister*[4]. Notably, both healthy males and females spanning various age ranges exhibit diverse bacterial taxa in midstream urine samples, including *Lactobacillus, Klebsiella, Corynebacterium*, and *Staphylococcus,* among others[37,38]. Gender-specific differences are discernible, likely influenced by physiological and hormonal variations, alongside differential excretion of urinary chemicals such as creatinine, citrate, calcium, and oxalate, which may modulate microbial colonization patterns [39]. Studies indicate that midstream urine samples from females demonstrate greater bacterial diversity compared to those from males, with Lactobacillus species prominently represented in fertile women alongside *Actinobacteria* and *Bacteroidetes* phyla[40]. Despite gender-specific distinctions, core genera such as *Lactobacillus, Corynebacterium*, and *Streptococcus* persist in the UT microbiome across genders and life stages, albeit in varying abundances [41,42]. Women bear a disproportionate burden of urinary tract infections (UTIs), with about 50% experiencing UTIs at some point in their lives, with heightened risks among postmenopausal and elderly individuals[43,44]. Conditions like interstitial cystitis/bladder pain syndrome (IC/BPS) and UT obstructions also influence UT microbiome dynamics, with pathogenic bacteria associated with UTIs and structural abnormalities disrupting microbial composition[45].

Beyond host-related factors, medications, dietary patterns, hygiene practices, and environmental variables exert substantial influence on the UT microbiome. Medications like antibiotics and cancer treatments, dietary habits, fluid intake, hygiene practices, and environmental exposures all shape microbial ecology and colonization patterns[46,47]. Comprehensive understanding of these multifaceted influences is crucial for elucidating the urinary microbiome's implications in health and disease and devising strategies for UT health maintenance.

4. Role in Health and Disease

The UT microbiome serves a pivotal role in maintaining health by contributing to protective mechanisms akin to those observed in the gut microbiome. Through niche occupation and resource competition, beneficial bacteria inhibit the colonization of pathogenic counterparts, thereby preventing microbial imbalances and UT infections [21]. Additionally, interactions between the UT

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microbiome and the local immune system are instrumental in modulating immune activity, crucial for preserving immunological homeostasis and averting inflammation or autoimmune responses[48–50]. Metabolic versatility allows microbes to metabolize various substances, including host-produced molecules and dietary components, affecting the nutritional and chemical landscape of the surrounding environment. The composition of the UT microbiome can influence the body response to treatments, such as medications for UT infections, suggesting the potential for developing more effective therapeutic interventions by elucidating microbiota functions in treatment outcomes[51]. Alterations in UT microbiome composition may serve as biomarkers for specific diseases or conditions, offering insights into personalized treatment strategies and providing valuable diagnostic or prognostic information[52]. The UT microbiome exhibits lower pH levels in a healthy state, which can rise in disease states. Presence of various probiotic strains like *Lactobacillus rhamnosus, Lactobacillus fermentum*, and *Lactobacillus reuteri* are beneficial and exert their antibacterial activity primarily through the production of lactic acid during carbohydrate metabolism in the epithelium's glycosaminoglycan layer. The resulting decrease in pH (≤4.5) creates an inhospitable environment for many pathogenic bacteria (Figure 1)[53]. Additionally, they produce other antibacterial substances like hydrogen peroxide and bacteriocin. Hence, probiotics and prebiotics represent promising avenues for UT illness management alongside personalized antibiotic therapies, informed by a deeper understanding of urine microbiome dynamics and composition [53].

Changes in the composition of the UT microbiome, known as dysbiosis, have been linked to various diseases, including UTIs, interstitial cystitis or bladder pain syndrome (IC/BPS), overactive bladder syndrome (OAB), urinary incontinence (UI), and kidney stones[28]. Additionally, the gut microbiota plays a significant role in regulating the development of certain UT illnesses through a mechanism known as the gut-bladder axis[54,55]. NGS studies have revealed a strong causal relationship between these disorders and the influence of the microbiome on both the bladder and gut. Consequently, dysbiosis of both the gut and urine microbiota may represent a significant contributing factor in the development of diseases affecting the urinary system [56]. Some of these have been elaborated below to highlight the role of microbiota in disease.

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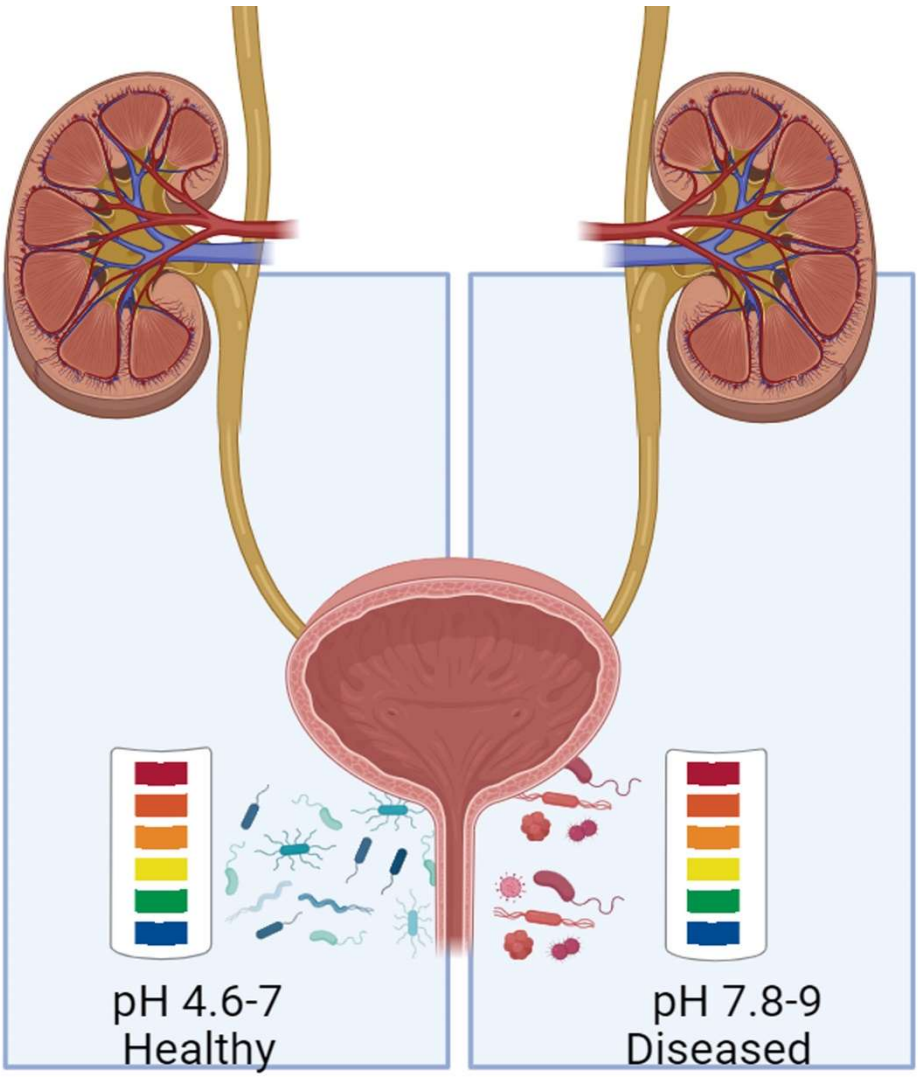

Figure 1. UT microbiome in healthy state showing lower pH and in disease state showing high pH.

UTIs

UTIs can generally be classified as higher UTIs or lower UTIs. Upper UTIs involve infections in the kidneys or ureters, while lower UTIs refer to infections in the bladder or urethra[57]. *E. coli* bacteria are the main cause of UTIs[58]. Although this bacterium is naturally occurring in human bodies, it intermittently finds a way into the UT through the urethra and begins to proliferate in the bladder and ureters, leading to UT infections[59]. Another concept, referred to as the gut-vaginal bladder axis, suggests that when UTI causing strains enter the bladder by the gastrointestinal tract or vagina, they engage in polyinfection and quorum sensing [60]. Further evidence supports the role of vaginal microbiota in regulating UTI as well, because women with vaginosis caused by anaerobic *G. vaginalis* overgrowth have a higher risk of UTI than women with healthy microbial communities dominated by *Lactobacillus* [61]. In every age group, women are more likely than males to get an uncomplicated UTI. Age-matched men report an incidence rate of roughly 0.01 per person/year, whereas young, sexually active women report incidence rates ranging from 0.5 to 0.7 per person/year[62]. There is now a lot of research being done on the connection between the compositional dynamics of the urinary microbiome and the prevalence of UTIs [63].

Exposure to *G. vaginalis* leads to the outflow of latent intracellular reservoirs of *E. coli* in the bladder, hence increasing the risk of potentially fatal *E. coli* infections[64,65]. Exposure to G. *vaginalis* is sufficient to induce renal damage that persists after the microbe is eliminated from the urine system, as well as bladder epithelial apoptosis and exfoliation[64]. Therefore, UTI-associated disease

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in humans cannot be explained by a single invasion of an exogenous pathogenic bacterium. The complexity of UTI-associated diseases in humans underscores the need to consider both urinary microbiota imbalance and polymicrobial pathogenic causes for a comprehensive understanding of UTIs [45,66]. Thus, addressing UTIs requires a multifaceted approach that acknowledges the interplay between host physiology, microbial communities, and infectious agents.

Interstitial Cystitis or Bladder Pain Syndrome (IC/BPS)

Interstitial cystitis or bladder pain syndrome (IC/BPS) is a perplexing urological illness characterized by urgency of urine and discomfort in the bladder[67]. While the exact cause of IC/BPS remains unknown, recent research suggests a potential link between the UT microbiome and the development of the condition[68–70]. While traditionally, the microbiological diagnosis of UTIs relied on culture techniques, which may not adequately capture the diverse microbial communities present in patients with IC/BPS, recent advancements in metagenomic analysis have provided insights into the role of the urinary microbiome in this condition [71,72]. Xu et al. investigating the microbiome of individuals with IC/BPS have revealed significant correlations between urinary microbiota composition (upregulation of four opportunistic pathogenic genera, i.e. *Serratia, Brevibacterium, Porphyromonas*, and *Citrobacter*) and symptomatology[71]. Utilizing metagenomic techniques, Zheng et al. have identified alterations in the urinary microbiome of females (abundance of *Lactobacillus* and *Escherichia-Shigella;* decreased *Bacteroides* and *Acinetobacter*) vs males with IC/BPS compared to healthy controls[73]. Ceprnja et al. have further elaborated the contributing role of Gammaproteobacteria in IC by metagenomics and prediction through generalized Lotka-Volterra modeling[74].

Overactive Bladder Syndrome (OAB)

Overactive bladder syndrome (OAB) is a chronic medical disorder that significantly impacts the quality of life for both men and women, characterized by urgency of urination, frequency, and nocturia, with or without urgent incontinence, in the absence of obvious illness[75]. The multifactorial nature of OAB complicates its understanding, as the underlying causes may vary among individuals[76]. Previously, it was allied with neurological factors impacting bladder but now research has revealed that low-grade bacterial colonization or dysbiosis (imbalance) in the urinary tract might contribute to OAB symptoms in some individuals. The microbiomes of healthy women without OAB symptoms and those with OAB have revealed significant differences in the microbial composition of the bladder. Siddiqui et al. have used 16s rRNA technique to identify *Streptococcus, Atopobium, Ureaplasma, Prevotella, Bacteroides* in the OAB impacted patient[77]. Hilt et al.[78] have shown presence of *Lactobacillus, Corynebacterium, Streptococcus, Actinomyces, Staphylococcus, Aerococcus, Gardnerella, Bifidobacterium,* and *Actinobaculum* by using culture dependent techniques alongside 16s rRNA sequencing study of four women suffering from OAB. While Lactobacillus was less prevalent in the urine of women with OAB compared to healthy controls, the presence of Proteus was more frequently observed in OAB patients[79]. Bacterial presence may trigger inflammation in the bladder, leading to hypersensitivity and OAB symptoms. Certain bacteria might alter nerve signaling pathways involved in bladder control[75]. Using 70 patients, Li et al. identified certain bacterial genera (e.g., *Porphyromona* and *Prevotella*) to be significantly correlated with severity of OAB sub-symptoms[80]. A systematic review analysis by Sze et al. shows that no study reveals identical microbiota abundance, even among healthy individuals[81]. OAB patients exhibit a reduced bacterial diversity compared to controls and overall microbiome composition depends on the specimen collection method and the metagenomic sequencing technique used. OAB urine microbiome is more susceptible to alterations from gut or vaginal influences compared to controls[81,82]. Not all OAB cases are linked to changed UT microbiota and studies have identified a connection between OAB and the gastrointestinal tract microbiota as well[61]. Alterations in the gut microbiome composition have been linked to OAB and daily urine urgency, with individuals experiencing OAB symptoms exhibiting less microbial diversity compared to non-OAB groups. Specifically, the abundance of Bifidobacteriaceae was significantly lower in individuals with OAB and daily urine urgency.

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Urinary Incontinence (UI)

UI refers to the involuntary loss of urine, a prevalent condition affecting millions worldwide[83]. While the causes of UI are diverse, a growing body of research suggests a complex interplay between the urinary tract microbiome and the development of UI, particularly urgency urinary incontinence (UUI)[84]. UUI has symptoms that resemble those of a urinary infection, including increased frequency and urgency of urination. Significant changes in the quantity and frequency of urinary microbiota have been discovered by both high-throughput sequencing and extended culture techniques [85]. A control cohort showed a decrease in *Lactobacillus* and an increase in *Gardnerella* in the UUI microbiome after using EQUC procedures to extract live bacteria from urine collected via transurethral catheter from women with UUI[86]. Culture revealed the presence of *Actinobaculum, Actinomyces, Aerococcus, Arthrobacter, Corynebacterium, Gardnerella, Oligella, Staphylococcus*, and *Streptococcus* in patients. *Lactobacillus gasseri* was more frequently detected in the UUI cohort, while *Lactobacillus crispatus* was most commonly found in controls[86]. *Lactobacillus* abundance was also allied with resistance to anticholinergic treatment for this condition[84]. Several investigations have suggested a potential connection between intestinal dysbiosis and UUI[61].

Kidney Stones

Kidney stones, also known as nephrolithiasis or renal calculi, are mineral deposits that form in the kidneys and can cause significant pain and discomfort when they obstruct urinary flow[87]. Nanobacteria have been linked to kidney stone formation, with 97.2% of the stones tested yielding positive results for nanobacteria[88]. Notably, only struvite stones exhibited the presence of common bacteria alongside nanobacteria. While apatite stones exhibited the highest nanobacteria antigen signals, the overall presence of nanobacteria was not affected by the stone type. In vitro experiments revealed that the isolated nanobacteria could indeed generate apatite stones, as demonstrated by the incorporation of calcium and strontium-85. Urease-producing bacteria, such as *Proteus mirabilis, Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Providentia stuartii, Serratia*, and *Morganella morganii*, are consistently associated with the formation and recurrence of struvite stones[89]. These bacteria produce urease, which breaks down urea, resulting in the formation of ammonia and carbon dioxide. This process leads to urine alkalinization and the subsequent formation of phosphate salts, contributing to stone formation in the kidneys. Moreover, there is a concurrent increase in acid-tolerant pathobionts among individuals with recurrent stone formation[90]. Additionally, specific enzymes involved in oxalate metabolism have been found to be elevated in those who suffer from kidney stones chronically.

Furthermore, the presence of biofilms, microbial communities encased in a protective matrix, on the surface of kidney stones may contribute to stone growth and recurrence. These biofilms can harbor bacteria and facilitate the adherence of crystals, promoting stone formation and providing a reservoir for recurrent infections [91]. When the urinary microbiome of kidney stone patients was investigated using 16S rRNA gene sequencing, it was found that the patients urine contained a different representation of bacteria linked to inflammation, such *as Acinetobacter*, and that the diversity of the urinary microbiota was significantly lower in these patients than in healthy controls. Thus, dysbiosis in the urinary and stomach microbiota appears to be a major factor in kidney stone formation, mediated by the rate at which oxalate is consumed or the control of the kidney's inflammatory response [92]. Certain bacteria in the gut and potentially the urinary tract may influence the breakdown and absorption of substances like oxalate, a major component of some kidney stones[93]. Clinical trials exploring the potential of using *O. formigenes* or its enzymes to decrease hyperoxaluria have exhibited encouraging findings. *In vivo* studies have demonstrated that *Lactobacillus* and *Bifidobacterium* species possess the capability to reduce oxalate levels[93].

Benign Prostatic Hyperplasia

Benign Prostatic Hyperplasia (BPH) is a condition characterized by the non-cancerous enlargement of the prostate gland, which can lead to urinary symptoms such as difficulty urinating,

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frequent urination, weak urine flow, and incomplete bladder emptying[94]. While BPH is primarily considered a condition related to changes in hormone levels and age, there is growing evidence suggesting a potential role for the microbiota in the development or exacerbation of BPH[95–97]. *Propionibacterium acnes*, commonly found in the skin microbiota and implicated in various inflammatory conditions like acne, has shown an association with BPH in some studies, suggesting a potential role in prostatic inflammation[98]. Okada et al. have also identified *Burkholderia as a culprit for BPH[99]. Sarkar et al.[100] have also reported Kocuria palustris and Cellvibrio mixtus to be notably enriched in samples from patients with BPH.* Jain *et al.* [101]revealed a unique microbial composition within BPH tissues, characterized by the notable presence of *E. coli* among other species such as *Micrococcus spp, coagulase-positive Staphylococcus, Bacteroidetes, Proteobacteria, Firmicutes, and Actinobacteria.* This finding suggests a potential role of these bacteria, particularly *E. coli*, in the inflammation and tissue damage associated with BPH. *In vitro* studies further demonstrated that *E.coli* associated with BPH can activate NF-κB signaling and induce DNA damage in prostate epithelial cells. Bajic et al. (2020) expanded the research, utilizing both mid-stream urine and transurethral catheterization samples. They utilized urine culture and 16S rRNA gene sequencing analysis, identifying *Streptococcus, Veillonella, Gardnerella, Staphylococcus,* and *Candida* as relevant microbiota[102]. They also found that an increase in the International Prostate Symptom Score (IPSS) was associated with significantly higher odds of detectable bacteria in catheterized urine, indicating the adequacy of catheterized urine in sampling the bladder microbiome

Glomerulonephritis

Glomerulonephritis, a condition characterized by inflammation in the kidney's glomeruli, can be triggered or exacerbated by certain microbial infections, particularly in cases of post-infectious glomerulonephritis[103]. Among the microbial agents responsible for this condition, Group A Streptococcus (*Streptococcus pyogenes*) is the most common culprit, often associated with throat or skin infections such as strep throat or impetigo, leading to what is known as post-streptococcal glomerulonephritis (PSGN)[103]. Although its incidence is now decreased in developed countries, it still occurs with notable frequency in densely populated and economically disadvantaged communities worldwide, where group A β-haemolytic streptococcal infections are prevalent[104]. Among children, PSGN remains the most common cause of acute glomerulonephritis. Bateman et al. [105]have stated that postinfectious glomerulonephritis represents an immune-mediated form of acute glomerulonephritis typically observed several weeks after an infection with *Streptococcus pyogenes*. Koyama et al.[106] have also reported its association with MRSA infection. It is hypothesized that post-MRSA glomerulonephritis may be induced by superantigens, leading to the production of high levels of cytokines and polyclonal activation of IgG and IgA. The formation of immune complexes containing IgA and IgG in the circulation subsequently contributes to the development of glomerulonephritis. Other bacteria, including *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,* and *Mycoplasma pneumoniae,* have also been linked to cases of post-infectious glomerulonephritis, albeit less frequently[107–109]. In post-infectious glomerulonephritis, the immune response elicited by these microbial infections results in the deposition of immune complexes within the glomeruli, leading to inflammation and kidney tissue damage. However, not all cases of glomerulonephritis are directly linked to microbial infections, as various forms of the disease have different underlying causes.

Urinary Tract Cancer

Urinary tract cancer encompasses a range of malignancies that can affect different parts of the urinary system, including the kidneys, bladder, ureters, and urethra. While the role of the microbiota in urinary tract cancer is an area of ongoing research, there is growing evidence suggesting that alterations in the urinary microbiota may be associated with the development or progression of certain types of urinary tract cancer[110–114]. These differences include alterations in the abundance of specific bacterial species or taxa, as well as changes in overall microbial diversity can lead to cancer. Certain microbial metabolites produced by dysbiotic urinary microbiota may have carcinogenic

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properties or influence tumor progression. For example, metabolites such as nitrosamines and aromatic amines, which can be derived from dietary sources or microbial metabolism, have been implicated in bladder carcinogenesis [115]. Three key components have been identified to represent the tumor-promoting effect of *E. coli* in this context[116]. Firstly, the contamination of bladder tissues by *E. coli* increases the carcinogenic potential of nitrosamine precursors, potentially due to an elevation in nitrite production by the bacteria and sustained synthesis of nitrosamine through in-situ nitrosamine formation. Secondly, *E. coli* contamination accelerates urothelial cell proliferation, which may enhance the mutagenic effects of the carcinogenic agent. Thirdly, prolonged exposure to oxidative and nitrosative stress leads to DNA damage and mutation. These findings highlight the multifaceted mechanisms through which *E. coli* contamination in bladder tissues can contribute to the progression of cancer.

Heidler et al. [117]studied kidney cancer microbiota using amplicon metagenomics and found *Aeromonas salmonicida, Pseudoalteromonas haloplanktis, Parageobacillus toebii, Trachelomonas volvocinopsis, Mycoplasma mycoides,* and *Halomicrobium mukohataei* as common in the cancerous parts. Bacteria like *Cyanophora paradoxa, Spirosoma navajo, Phaeocystis antarctica, Euglena mutabilis,* and *Mycoplasma vulturii* were only found in the cancerous tissue. These bacteria can produce carcinogenic metabolites, induce chronic inflammation, or promote DNA damage, potentially contributing to carcinogenesis. However, the most extensively studied types of urinary tract cancer in relation to the microbiota is bladder cancer, where differences in the composition of the urinary microbiota between individuals with bladder cancer and healthy controls[118,119]. Increased abundance of certain bacteria, like *Proteobacteria* and *Fusobacteria*, has been linked to bladder cancer, while others like *Lactobacillus* may have protective effects. *E. coli* and other members of the Enterobacteriaceae family, have also been associated with bladder cancer[120].

Autoimmune Diseases

The urinary tract system organs are also affected by autoimmune diseases (Table 1). Although not all of them have been allied with impaired microbiota of urinary tract, there is evidence supporting role of bacteria in infection and autoimmunity trigger in some of the diseases, such as pyelonephritis.

Table 1. Autoimmune diseases associated with urinary tract organs.

Autoimmune disease	Primary organ/body part affected	Autoantibodies	Reference
Goodpasture syndrome	Kidneys, lungs	Anti-GBM antibodies	[121]
IgA nephropathy	Kidneys	IgA autoantibodies, anti-OMHP antibodies	[122,123]
IgA vasculitis	Kidneys, lungs	IgA1 autoantibody	[124]
Membranous nephropathy	Kidneys	Anti-PLA2R antibodies	[125]

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Lupus nephritis	Kidneys	Anti-dsDNA, Anti-Sm, Anti-nuclear antibodies	[126]
Interstitial nephritis	Kidneys	Various autoantibodies	[127]
Interstitial cystitis	Bladder	Anti-urothelial and anti-nuclear antibodies	[128]
Primary sclerosing cholangitis	Bile ducts, can affect gallbladder	ANCA, Anti-mitochondrial antibodies	[129]
Pyelonephritis	kidney	Tamm-Horsfall protein antibodies, Tubulointerstitial nephritis antigen protein antibody	[130,131]
Xanthogranulomatous pyelonephritis	kidney	-	-
Prostatitis	Prostate gland	Prostate tissue immunodominant antigen (HPTIAs) protein antibodies	[132]

Acute pyelonephritis is characterized by fever, back-pain, pus and foul smell of urine. Its primary culprits have been identified as *E. coli* and *K. pneumoniae* [133]. *G. vaginalis* abundance also exposes women to pyelonephritis[134]. Research has also shown that *P. mirabilis* and uropathogenic *E. coli* cooperate through metabolic interactions, allowing them to better colonize and persist within the urinary tract, potentially increasing the risk of pyelonephritis[135,136]. Keogh *et al*. (2016) revealed that in iron-limited environment, *E. faecalis* secretes L-ornithine to aid uropathogenic *E. coli* in acquiring iron, a nutrient crucial for bacterial growth and worsen infection during UTI, leading to pyelonephritis[137]. This suggests that these bacterial interactions can worsen infections. Staining of glomerular structures has revealed presence of *H. pylori* antigens in 100% of kidney samples from IgA vasculitis patients[138]. *Haemophilus parainfluenzae* has been detected in 35% of IgA vasculitis kidney biopsies, with a much lower prevalence (4%) in biopsies from patients with other kidney diseases[139]. Nephritis-associated plasmin receptor (NAPI-r), a group A streptococcal antigen has been detected in some patients with IgA vasculitis[140] as well as IgA nephropathy[141]. Kidney biopsies of some IgA nephropathy patients have also shown evidence of E. coli and H. influenza. This suggests that a direct bacterial infection with these species might contribute to IgA nephropathy and the exposure might trigger an autoimmune response that mistakenly attacks the glomeruli (filtering units) in the kidneys, leading to IgA nephropathy. H. pylori has also been implicated in the membranous nephropathy in almost two third of patients and some patients in Lupus nephritis [138].

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However the pathogenic nature of the *H. pylori* presence remains yet to be elucidated in Lupus nephritis[142].

Aerobic culture of the seminal fluid of prostatitis patients revealed Enterobacteriaceae, enterococci and Staphylococcus aureus inpatients and absent from control group[143]. Nickel et al. [144]reported Burkholderia cenocepacia over represented in chronic prostatitis, using initial and mid-stream urine. Shoskes et al. [145]used urine DNA to identify higher counts of Clostridia compared with controls in prostatitis patients. Mandar et al. [146]further revealed that men with prostatitis had lower levels of health-promoting lactobacilli and a more diverse bacterial community (including proteobacteria) compared to healthy men[147].

Therapeutic Implications

The study of the urinary tract microbiota has significant therapeutic implications, particularly in the diagnosis, treatment, and prevention of UTIs and other urinary tract disorders[53]. Understanding the factors that influence the composition and stability of the urinary microbiota can inform preventive strategies for UTIs and other urinary tract disorders. Lifestyle modifications, dietary interventions, and hygiene practices aimed at promoting a healthy urinary microbiota may help reduce the risk of UTIs and maintain urinary tract health[148]. The development of UTI microbiome-targeted medicines has been encouraged by the discovery of the urinary microbiome and its link to disease. Antibacterial medication is the most widely used treatment for UTIs but broad-spectrum antibiotic treatment may have a deleterious effect on the beneficial bacterial flora of the host and leads to the pathogenic bacterial selective expansion. For some antimicrobials, prolonged usage of the drug can result in up to 50% of cases of bacterial resistance [53]. In an attempt to lower rates of antibiotic resistance and recurring infections, probiotics, which replicate purported defenses bolstered by the normal microbiome, have emerged as a therapeutic alternative for the prevention and treatment of UTIs [149]. The restoration of *Lactobacillus* communities is linked, in part, to the development of novel therapeutic approaches for urinary disorders[18]. Probiotics offer a promising avenue for restoring UT microbial balance and work in concert with the host immune system to produce compounds like vitamins and immunomodulators, acidify the mucosal surface and inhibit pathogen attachment [150,151]. Clinical studies have shown promising results, demonstrating the efficacy of probiotics in preventing and treating UTIs (Table 2) [152–156].

Table 2. Interventional or observational clinical trials for UTI prevention, involving the use of probiotics. Data obtained from Clinicaltrials.gov (retrieved 1 June 2024).

#	Name	Status	NCT ID	Phase	Drugs
1	Lactobacillus Probiotic for Prevention of UTI	Completed	NCT03151967	Phase 2, Phase 3	*Lactobacillus crispatus* CTV-05; Placebo
2	Targeted Pathogen Replacement With Novel Probiotic Treatment for Prevention of Recurrent UTIs in Children	Completed	NCT01696227	-	Nissle 1917
3	Observational Study Evaluating the Number of Symptomatic Cystitis-like Episodes and Urinary Comfort of Women Consuming Cranberry, Cinnamon and Probiotic Strain Extracts	Completed	NCT04987164	-	Cranberry, Cinnamon, Probiotics

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4	Probiotic and Effects on Multi-Drug Resistant Urinary Tract Infection	Completed	NCT03644966	-	*Bifidobacterium infantis*, Antibiotics
5	A Double-blinded, Randomized, Placebo-controlled, Parallel-group Study Evaluating the Effect of the Probiotic on Recurrent Urinary Tract Infection (UTI) in Adult Women Recently Treated for UTI.	Completed	NCT03366077	-	Probiotic (name not mentioned)
6	Preventing Urinary Tract Infections in Infants and Young Children With Probiotic E. Coli Nissle:	Recruiting	NCT04608851	Phase 4	*E. coli* Nissle
7	A Novel Probiotic-antibiotic Combination to Prevent Recurrent Urinary Tract Infections	Recruiting	NCT06149676	Early Phase 1	*Saccharomyces Boulardii* 250 MG [Florastor]
8	Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of a Probiotic on the Urinary Tract Microbiota in Women With Recurrent Urinary Tract Infections (rUTI).	Recruiting	NCT05895578	-	Probiotic (name not mentioned) and antibiotic
9	A Clinical Trial to Determine the Extent to Which Probiotic Therapy Reduces Side Effects of Antibiotic Prophylaxis in Pediatric Neurogenic Bladder Patients With a History of Recurrent Urinary Tract Infections	Unknown status	NCT02044965	Phase 1, Phase 2	Trimethoprim; sulfamethoxazole; *L. rhamnosus* GR-1 and *L. reuteri* RC-14
10	Probiotics/Lactobacillus as a Prophylactic Aid in Recurrent Bacterial Cystitis in Women. A Randomized, Prospective, Double-Blinded, Placebo Controlled, Multi-Center Study.	Unknown status	NCT00781625	-	UREX-Cap-5 (*Lactobacillus rhamnosus* GR-1, *Lactobacillus reuteri* RC-14)
11	Effectiveness of Prophylaxis of Urinary Tract Infections in Children With a Probiotic Containing Lactobacillus Rhamnosus PL1 and Lactobacillus Plantarum PM1, a Randomised Clinical Trial	Unknown status	NCT03462160	-	*Lactobacillus Rhamnosus* PL1 and *Lactobacillus Plantarum* PM1

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If specific bacterial components are found to trigger autoimmune responses, research could focus on developing therapies that target these specific immune cells or pathways to prevent them from attacking healthy tissues. The role of iron acquisition by bacteria like *E. faecalis* suggests that iron chelation therapies could be also explored as a way to starve harmful bacteria and potentially reduce their ability to worsen infections. The preservation of mucosal immunological homeostasis in the UT may be improved by microbiome transfer and restoration therapies that involve the inoculation of artificial communities of health-associated Lactobacilli. Probiotics can help restore the balance of the urinary microbiome, potentially reducing the risk of urinary tract infections and promoting overall urinary tract health [8]. Certain Lactobacillus strains, including *L. rhamnosus* GR1, *L. fermentum* RC-14, and *L. reuteri* B-54, have demonstrated efficacy in treating UTIs[157,158]. This positive impact is attributed to the release of lactic acid into the environment as these bacteria break down carbohydrates in the glycosaminoglycan layer of the lower urinary tract epithelium. Lactic acid contributes significantly to the antibacterial activity of *Lactobacillus* strains by lowering the pH (below 4.5), creating an unfavorable environment for most pathogenic bacteria[159]. Additionally, *Lactobacillus* species produce other metabolites such as bacteriocins and hydrogen peroxide, further enhancing their antimicrobial properties[160]. *Lactobacillus* species significantly *suppress E. coli* and help host urothelial cells produce type I interferon, which modifies the innate immunity in the bladder to produce a protective milieu for the host[120]. *Lactobacilli* leads to a change in the proportion of bacteria towards a more beneficial microbial makeup that guard against UTIs [161].

In addition to probiotics, exploring competitive alternatives like antibiotics is vital for addressing UTIs[162]. Competitive inhibition is where beneficial microorganisms outcompete uropathogens for resources, presents an effective strategy. These include bacteriocins and bacteriophages, which target specific bacterial strains without disrupting the UT microbiome equilibrium[163]. Human cathelicidins, defensins, and bacteriocins are examples of antimicrobial peptides that are secreted from the urothelium and have both antibacterial activity and immunomodulatory effects[164,165]. The presence of *H. pylori* in some autoimmune kidney diseases warrants further investigation and if a causal link is established, eradication of *H. pylori* with antibiotics could be a therapeutic option for some patients. Studies reporting synergism between strains such as *E. coli* and other bacteria highlight how bacterial cooperation can worsen infections. Understanding these interactions could lead to the development of drugs that disrupt these partnerships and potentially prevent infections that might trigger autoimmune responses.

To counter increasing multidrug resistance, bacteriocins and natural product based inhibitors to destroy rival organisms could be explored. An example of bacteriocin is colicins, which cause harm to target cells by inhibiting the formation of peptidoglycan, cellular nuclease degradation and membrane permeabilization via voltage-dependent channels[166]. They have been described as a means of preventing and lessening the development of biofilm on urinary catheters [167]. Several studies have reported successful outcomes using bacteriophages in treating UTIs caused by antibiotic-resistant bacteria. Bao *et al.* [168]have reported a synergistic approach involving non-active antibiotics and bacteriophages has been successfully employed to treat recurrent UTIs caused by extensively drug-resistant *Klebsiella pneumoniae*. This approach highlights the potential of combining different antimicrobial strategies to combat multidrug-resistant pathogens and underscores the importance of exploring novel treatment modalities in the face of increasing antibiotic resistance. Khawaldeh et al. have reported the successful treatment of a patient with a complicated UTI caused by multidrug-resistant *Pseudomonas aeruginosa*, which was resistant to antibiotics including gentamicin, ceftazidime, ciprofloxacin, and meropenem. Bacteriophages have also effectively removed mature biofilms formed by bacteria such as *Escherichia coli* and *Proteus mirabilis*, which are responsible for catheter-associated UTIs[169].

Preventive therapies include cranberry supplement containing compounds such as proanthocyanidins that may help prevent bacteria, particularly *Escherichia coli*, from adhering to the urinary tract lining[170]. Certain supplements or foods, such as vitamin C or foods high in citric acid, can acidify urine, creating an environment less conducive to bacterial growth[171]. Additionally, research suggests that D-Mannose may be effective in preventing UTIs and reducing the recurrence

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rate by interfering with the attachment of uropathogenic bacteria to UT epithelial cells (Figure 2)[172]. D-Mannose is a naturally occurring sugar that can inhibit bacterial adhesion to the UT lining and clinical studies have demonstrated the efficacy of D-Mannose supplementation in reducing UTI symptoms and recurrence, making it a promising alternative or adjunct therapy to antibiotics[173]. In addition, D-Mannose has been investigated for its potential in restoring UT microbiota balance. By preventing bacterial adhesion and colonization, D-Mannose may help maintain a healthy UT microbiota composition, reducing the risk of dysbiosis and UTI recurrence.

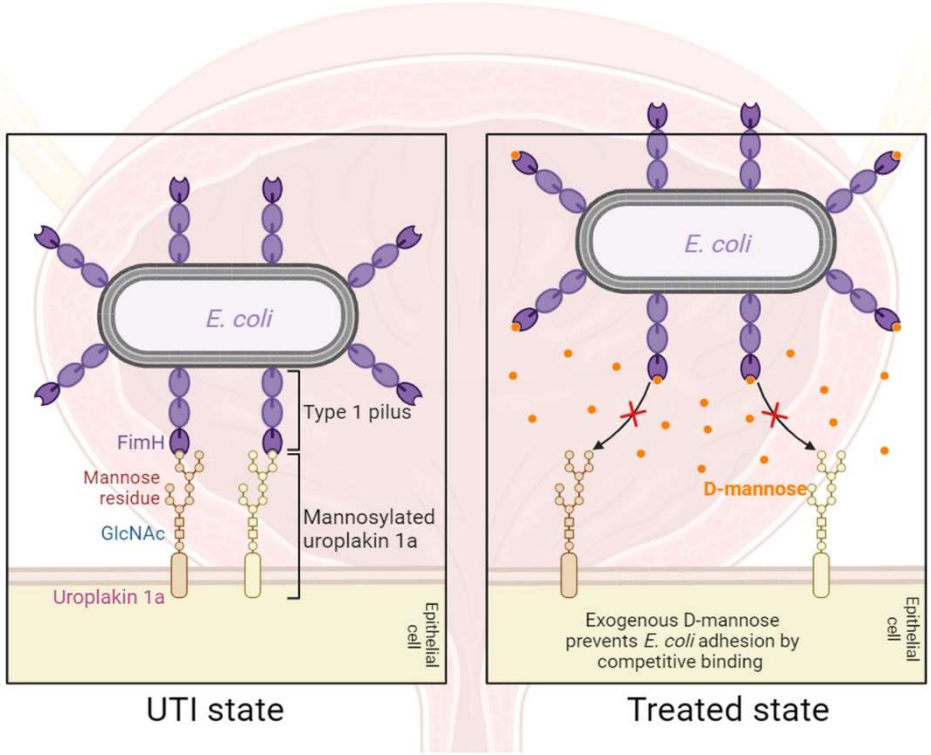

Figure 2. Competitive inhibition of *E. coli* adhesion by D-Mannose.

Future Perspective and Challenges

In future, microbiome studies have the potential to revolutionize the management of UTIs by offering personalized, community-based approaches. Understanding the normal urinary microbiome could aid in identifying microbial imbalances or dysbiosis that predispose individuals to UTIs, allowing for early intervention or prevention strategies. Co-occurrence network analysis to identify microbial species that frequently appear together to find cooperative/synergistic interactions could also be helpful. Culture independent methods have helped us gain insights at a deeper level but characterizing the diversity of microbes causing asymptomatic bacteriuria versus symptomatic infection could lead to more targeted treatment approaches, recognizing that not all bacteria need to be treated equally. Moreover, we also need long-term implications of antibiotic exposure on the urinary microbiome and recurrent infections need better characterization to optimize stewardship and prevent unintended consequences. Investigating microbial interactions and community dynamics may inform combination or sequential therapy approaches, enhancing treatment efficacy. Additionally, tracking microbial reservoirs could help eradicate sources of reinfection, particularly for recurrent UTIs associated with the re-emergence of previous infecting strains. Probiotics, synbiotics and phage therapy could be used to restore microbiome balance and train the immune system for long-term UTI prevention.

There are some challenges associated with UT microbiome research that need to be overcome in future. One challenge lies in standardizing urine collection and processing methods to ensure

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consistency and reproducibility across studies. Variations in collection techniques and laboratory protocols can introduce bias and affect the comparability of results. Standardizing these procedures will require collaboration among researchers, clinicians, and laboratory professionals to establish consensus guidelines and best practices. Another challenge is the need for robust computational analytics to analyze and interpret complex microbiome data effectively. Advances in bioinformatics tools and computational algorithms are essential for processing large-scale microbiome datasets, identifying microbial signatures associated with UTIs, and elucidating underlying mechanisms. Collaborative efforts between computational biologists, microbiologists, and clinicians are crucial for developing sophisticated analytical approaches and integrating multi-omics data for comprehensive insights. Longitudinal studies should also be conducted to enable researchers to track dynamic shifts in the urinary microbiome composition in response to various factors, including antibiotic treatment, lifestyle changes, and disease progression. This will help identify biomarkers predictive of UTI recurrence and treatment response, facilitating personalized risk prediction and prevention strategies.

Establishing causality between the urinary microbiota and UTI pathogenesis remains a complex and challenging task. While observational studies have identified associations between microbial dysbiosis and UTIs, establishing causality requires rigorous experimental designs, including intervention studies and mechanistic investigations. Critically appraising current evidence and addressing methodological limitations are essential steps toward elucidating the causal role of the microbiota in UTI pathogenesis. In addition, collaborative research efforts combining microbiome profiling, metabolomics, and immunological studies are essential for validating association and translating into clinical applications. We primarily focused on bacterial associations, but other aspects of the urinary tract microbiome, like fungi or viruses, might also play a role and need further investigation.

To facilitate standardized approaches and open data sharing in UT microbiome research, proposing frameworks and fostering multidisciplinary collaborations are imperative. Establishing consortia and research networks dedicated to UTI microbiome research can promote data harmonization, protocol standardization, and knowledge exchange among researchers worldwide. By fostering a collaborative ecosystem, we can overcome challenges, accelerate scientific discoveries, and ultimately improve UTI prevention, diagnosis, and treatment outcomes.

Conclusion

The urinary tract (UT) microbiome is a dynamic ecosystem that plays a significant role in both UT health and disease. Advancements in various culturing techniques and metagenomic sequencing have greatly contributed to our understanding of the UT microbiome community and its implications for disease. The UT microbiome is involved in a range of functions related to urinary tract health and pathology. By leveraging insights from microbiome research, these approaches have the potential to improve treatment outcomes and overcome challenges associated with antibiotic resistance in managing UTIs and other UT-related conditions. Novel therapeutic approaches utilizing microbiomes as probiotics or competitive alternatives show promise in minimizing UT microbiome-related diseases. Additionally, antimicrobial proteins offer supplementary therapeutic benefits to address antibiotic resistance in UT-related conditions. These innovative therapeutic strategies aim to restore microbial balance in the UT, potentially reducing the incidence of UTIs and other urinary tract-related disorders. Further research into the composition, dynamics, and functional significance of the UT microbiome is essential to fully comprehend its role in disease pathogenesis and to identify potential intervention targets. Other challenges in standardizing urine collection/processing methods, computational analytics, and establishing causality necessitate multidisciplinary collaborations for developing consensus guidelines, advanced analytical tools and translation of findings to clinical relevance.

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