

Integrating Antibacterial Drugs with Berberine and Non-Antibiotic Approaches in the Management of Recurrent Urinary Tract Infections in Male Patients

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ABSTRACT

Background

Recurrent urinary tract infections (rUTIs) represent a significant public health concern, contributing to considerable morbidity, diminished quality of life, and escalating healthcare costs. Conventional management of rUTIs often relies heavily on repeated antibiotic therapy, which can promote inappropriate usage and accelerate the emergence of antimicrobial resistance (AMR). This growing crisis underscores the urgent need to investigate **non-antibiotic interventions** that can prevent infection recurrence while preserving the efficacy of existing antibiotics.

Aim

This study aimed to evaluate the role of **berberine** as a non-antibiotic therapeutic agent in the prevention and management of rUTIs, with a particular focus on male patients, and to explore its potential as an adjunct to conventional antibiotic therapy.

Methodology

D-mannose was synthesized using both **biological fermentation** and **chemical catalysis** methods. Berberine was extracted via a methanol-ethyl acetate procedure and subsequently purified using **flash column chromatography**. In addition, a comprehensive literature review was conducted to assess other non-antibiotic interventions, including **probiotics, methenamine hippurate, urinary alkalization, hormonal therapy, and behavioral modifications**. The review focused on the mechanisms of action, clinical efficacy, and safety profiles of these interventions.

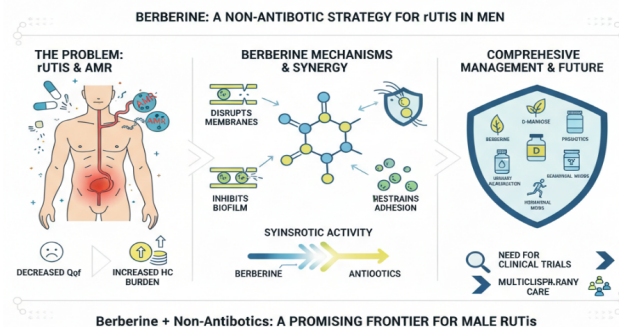
Results

Berberine demonstrated **broad-spectrum antimicrobial activity**, effectively targeting both Gram-positive and Gram-negative bacteria. Mechanistically, it disrupts bacterial cell membranes, inhibits biofilm formation, and prevents bacterial adhesion to the urinary epithelium. Importantly, berberine exhibited **synergistic effects with multiple classes of antibiotics**, enhancing their clinical efficacy when used as an adjuvant therapy.

Keywords: r-UTIs, non-antibiotic approaches, berberine, antibiotics, antimicrobial, broad-spectrum, methenamine.

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1. INTRODUCTION

A urinary tract infection (UTI) is a clinically significant inflammatory condition that influences various anatomical segments of the human urinary framework. These infections are typically classified based on their location: lower urinary tract contaminations, commonly referred to as **cystitis**, primarily influence the bladder or the urethra, whereas upper urinary tract diseases, known as **pyelonephritis**, can potentially hurt or damage the renal parenchyma of the kidney.

A lower urinary tract contamination is frequently characterized and shown by a cluster of distressing indications such as persistent suprapubic distress, significantly agonizing urination (dysuria), and an overwhelming, pressing urge to pee indeed when the bladder is entirely purge. In any case, the indications of a more severe kidney contamination are traditionally more systemic and debilitating in nature; these ordinarily incorporate high fever, chills, or acute flank torment in expansion to the existing localized side effects of a lower urinary tract disease [1]. While the presence of blood within the pee is an unprecedented event in routine cases, it can occur as a sign of significant mucosal irritation. It is important to note that these clinical indications may be notably dubious, subtle, or nonspecific in individuals at the extremes of age (i.e., those who are amazingly youthful or the elderly and ancient), often making a prompt diagnosis more challenging for clinicians [2].

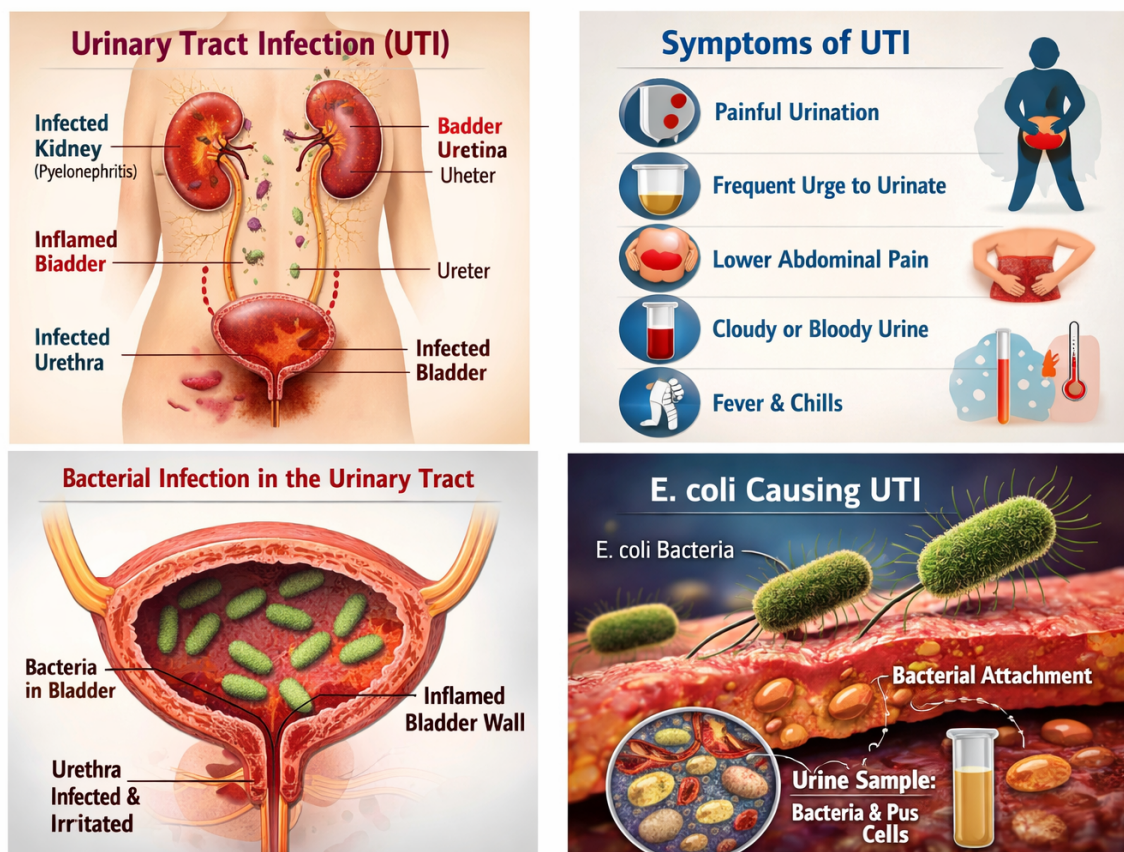
UTI can be classified into various types:

1.1.1. Uncomplicated UTI

The great majority of instances of uncomplicated urinary tract infection (UTI) are caused by specific bacterial pathogens that gain access to and proliferate within the urinary system. The lower urinary tract comprises the bladder and the urethra, which are the most commonly involved anatomical sites in uncomplicated infections. UTIs that primarily affect the bladder are often referred to as **cystitis** or **bladder infections**, and this form represents the most prevalent type of UTI encountered in clinical practice.

Uncomplicated UTIs typically occur in individuals with a structurally and functionally normal urinary tract and without significant underlying comorbidities or immunosuppression. These infections are usually acute in onset and are characterized by localized symptoms such as increased urinary frequency, urgency, dysuria, suprapubic discomfort, and cloudy or malodorous urine. Systemic manifestations are generally absent, distinguishing uncomplicated UTIs from more severe or complicated forms involving the upper urinary tract.

Because uncomplicated UTIs are most often limited to the lower urinary tract, they tend to respond well to appropriate antimicrobial therapy and have a favorable prognosis. Early recognition and timely management are important to alleviate symptoms, prevent bacterial persistence, and reduce the risk of recurrence or progression to more severe infection.



UTI infection. Source: <https://nycgyne.com/we-treat/urinary-tract-infection-uti/>

Figure 1. Pathophysiology, symptoms, and bacterial etiology of urinary tract infection (UTI), highlighting bladder, urethral, and renal involvement and the predominant role of *Escherichia coli*. [46].

Causes

Uncomplicated urinary tract infections (UTIs) are predominantly caused by specific bacterial strains that have a high affinity for the urinary tract epithelium. The most common pathogens include *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., and *Enterococcus* spp. Among these, *E. coli* and *Klebsiella* are responsible for the majority of uncomplicated UTI cases, accounting for a significant proportion of infections observed in both community and outpatient settings. These bacteria typically originate from the gastrointestinal tract and gain access to the urinary tract through colonization of the periurethral area, followed by ascension into the bladder.

Factors that predispose individuals to these infections include poor perineal hygiene, urinary stasis, sexual activity, and anatomical variations in the urinary tract. Additionally, the ability of these pathogens to adhere to the urothelial lining, evade host immune defenses, and form biofilms contributes to their virulence and recurrence potential. Understanding the microbial etiology of uncomplicated UTIs is critical for developing targeted preventive and therapeutic strategies, including both antibiotic and non-antibiotic approaches [1].

1.1.2. Complicated UTI

Any UTI that does not fulfill the criteria for an uncomplicated UTI is classified as a **complicated UTI**. This classification is typically applied when the infection is more difficult to treat, is associated with underlying anatomical or functional abnormalities of the urinary tract, or carries a higher risk of adverse clinical outcomes. Complicated UTIs often occur in patients with predisposing factors such as urinary tract obstruction, indwelling urinary catheters, renal calculi, neurogenic bladder, immunosuppression, diabetes mellitus, or chronic kidney disease.

A UTI may also be deemed complicated if it is caused by **atypical or multidrug-resistant pathogens** that are not commonly associated with uncomplicated infections, which can limit therapeutic options and necessitate prolonged or parenteral antimicrobial therapy [3]. In addition, infections involving the upper urinary tract, such as pyelonephritis, or UTIs occurring in male patients are frequently categorized as complicated due to their increased likelihood of recurrence, treatment failure, and progression to systemic infection.

Etiology

The pathogens responsible for complicated UTIs often include those commonly implicated in uncomplicated cases, such as *Escherichia coli*. However, complicated UTIs may also involve a broader range of microorganisms, including multiple bacterial species and, in some cases, fungal organisms such as *Candida* spp [4]. These infections may be polymicrobial, particularly in patients with indwelling urinary devices or prolonged hospital exposure. Notably, certain bacterial strains involved in complicated UTIs may exhibit resistance to standard antibiotic therapies, posing additional challenges to effective treatment [5]. The emergence of multidrug-resistant organisms further complicates management and highlights the need for accurate microbial identification and susceptibility testing. Understanding the diverse etiological agents involved in complicated UTIs is essential for optimizing therapeutic outcomes and reducing the risk of treatment failure.

1.2 Recurrent Urinary Tract Infection

Recurrent urinary tract infections (rUTIs) are a common and clinically significant problem, representing a substantial burden on affected individuals as well as on public healthcare systems worldwide. These infections are characterized by repeated episodes of UTIs over a defined period and may significantly

impair quality of life due to persistent symptoms, frequent medical visits, and repeated exposure to antimicrobial agents. While rUTIs can involve both the upper and lower urinary tracts, repeated infections affecting the upper urinary tract are of particular concern, as they may reflect underlying structural abnormalities, functional impairments, or host-related risk factors that contribute to a more complex disease etiology. Such cases require careful diagnostic evaluation and long-term management strategies to prevent renal damage and other serious complications [6].

Although antibiotics have long been regarded as the cornerstone of UTI treatment and are generally highly effective in achieving symptomatic relief and microbial eradication, their extensive and sometimes inappropriate use has contributed substantially to the global rise in antimicrobial resistance. The frequent recurrence of UTIs often results in repeated antibiotic courses, increasing selective pressure on uropathogens. It is estimated that approximately 20% to 50% of antibiotic prescriptions for acute inpatient care are unnecessary or suboptimal, further exacerbating resistance and reducing the long-term effectiveness of available antimicrobial agents [7].

In response to these challenges, antimicrobial stewardship programs have been widely implemented to promote the judicious use of antibiotics across healthcare settings. These programs aim to optimize antimicrobial prescribing practices by ensuring that patients receive the most appropriate drug, dose, and duration of therapy. In addition to improving clinical outcomes, stewardship initiatives emphasize the use of cost-effective treatments that are safe for patients and environmentally sustainable. A central objective of these programs is the reduction of antibiotic overuse, as excessive or inappropriate exposure to antibiotics can lead to toxic effects on the body, the selection of more virulent or aggressive organisms, the emergence of resistant bacterial strains, and the development of healthcare-associated infections such as *Clostridium difficile* colitis [8].

Recognizing the severity of antimicrobial resistance as a global health threat, the World Health Organization (WHO) has established a Global Action Plan to combat antimicrobial resistance (AMR), identifying AMR as one of the ten most critical health challenges facing the world today. The implementation of these recommendations has increased awareness among clinicians and researchers regarding the urgent need for alternative and adjunctive therapeutic strategies. As a result, there has been growing interest in the use of non-antibiotic interventions for both the prevention and management of UTIs, particularly in patients with recurrent infections, in an effort to reduce antibiotic reliance while maintaining effective clinical outcomes [9].

Signs and Symptoms

Individuals who experience recurrent urinary tract infections (rUTIs) may recognize a wide range of urinary and systemic signs and symptoms, which can vary in severity depending on the frequency of infection, the causative organism, and the presence of underlying risk factors. Commonly reported symptoms include:

- Frequent urination, often characterized by the need to void more frequently than usual, which may also include urinating during the night (nocturia), leading to sleep disturbance and reduced quality of life.
- A strong, sudden, and sometimes difficult-to-control urge to urinate, which may occur even when the bladder contains only a small volume of urine.
- A burning sensation or pain during urination (dysuria), reflecting inflammation or irritation of the urethral and bladder mucosa.
- Urine that appears cloudy, dark, or has visible blood (hematuria), which may indicate infection-associated inflammation or mucosal damage.
- A sensation of pressure, heaviness, or pain in the lower abdomen or pelvic region, commonly associated with bladder involvement.

- Difficulty initiating urination or a feeling of incomplete bladder emptying, which may contribute to urinary stasis and further increase the risk of recurrence.
- General malaise, including fatigue, body aches, low-grade fever, or an overall feeling of discomfort, particularly during active infection episodes.

Repetitive UTIs can sometimes lead to serious clinical consequences, especially when infections are inadequately treated or frequently recur. These complications may include ascending kidney infections (pyelonephritis), progression to chronic kidney disease, development of sepsis, and, in pregnant individuals, an increased risk of premature delivery and adverse pregnancy outcomes. Such complications highlight the importance of early diagnosis, appropriate management, and preventive strategies.

In infants and children, UTIs often present with atypical and nonspecific symptoms, such as unexplained fever, vomiting, irritability, poor feeding, and decreased activity levels. These nonspecific manifestations can complicate early recognition and delay diagnosis, potentially increasing the risk of renal involvement.

In women, the causes of recurrent UTIs are closely linked to several behavioral, anatomical, and physiological factors. These include sexual intercourse, the use of spermicidal agents, hormonal changes associated with menopause, and the migration of *Escherichia coli* from the rectal flora to the urinary tract, which facilitates repeated bacterial colonization and infection [10]. Understanding these contributing factors is essential for implementing targeted preventive and therapeutic strategies.

1.3 Chinese Herbal Medicine

Traditional Chinese Medicine (TCM) has long employed a variety of herbal formulations for the prevention and treatment of urinary tract infections (UTIs). These remedies are selected based on their ability to clear heat, eliminate dampness, reduce inflammation, and restore balance within the urinary system. Commonly used Chinese herbal formulations for UTIs include Er Xian Tang, Bai Tou Weng Tang, and San Jin Wan, each of which contains a combination of medicinal herbs believed to possess antimicrobial, anti-inflammatory, and immunomodulatory properties. These formulations have historically been used to alleviate urinary discomfort, reduce infection recurrence, and support overall urinary tract health, particularly in patients with chronic or recurrent infections.

Herbal Drug: Berberine (*Hydrastis canadensis*).

Berberine (BBR), also known as orangeroot or yellow puccoon, is a perennial herb native to North America and belongs to the Ranunculaceae family, commonly referred to as the buttercup family. It is a naturally occurring bioactive isoquinoline alkaloid that has gained significant attention due to its broad pharmacological properties. Berberine has been extensively utilized in both Traditional Chinese Medicine (TCM) and Ayurvedic medicine for centuries, particularly for the management of infectious, inflammatory, and metabolic disorders.

Berberine is primarily extracted from several medicinal plant species, including *Berberis aristata* (tree turmeric), *Berberis aquifolium* (Oregon grape), and *Coptis chinensis* (golden thread). Among these, *Coptis chinensis* is considered one of the richest natural sources of berberine. In addition, substantial amounts of berberine are obtained from the bark and roots of various plants such as *Coptis chinensis*, *Phellodendron amurense*, *Berberis vulgaris*, and *Berberis petiolaris* [11].

Within traditional medicinal systems, berberine has been valued for its antimicrobial, anti-inflammatory, and antioxidant activities. These properties make it particularly relevant in the management of UTIs, where bacterial infection and inflammation of the urinary tract play central roles. Its inclusion in several Chinese herbal formulations reflects its importance as a key therapeutic agent aimed at reducing pathogen load, alleviating

symptoms, and potentially lowering recurrence rates of urinary tract infections [11].



Hydrastis Canadensis: <https://gobotany.nativeplanttrust.org/species/hydrastis/canadensis/>

Figure 2: Hydrastis canadensis (Goldenseal), a medicinal plant traditionally used for its antimicrobial and urinary tract protective properties[43].

Pharmacological Properties of Berberine

Pharmacological studies have demonstrated that berberine possesses a broad-spectrum antimicrobial effect, making it effective against a wide range of bacterial, fungal, and protozoal pathogens. This antimicrobial potential is particularly valuable in the context of urinary tract infections, where both Gram-positive and Gram-negative organisms may be involved. The potent antibacterial activity of berberine has been linked to its ability to disrupt microbial DNA replication processes, interfere with nucleic acid synthesis, and inhibit essential enzymatic functions required for bacterial survival. In addition, berberine has been shown to suppress quorum sensing mechanisms, which are critical for bacterial communication, biofilm formation, and virulence expression. By targeting quorum sensing pathways, berberine reduces bacterial colonization and limits the persistence of infection, especially in recurrent and chronic cases [12].

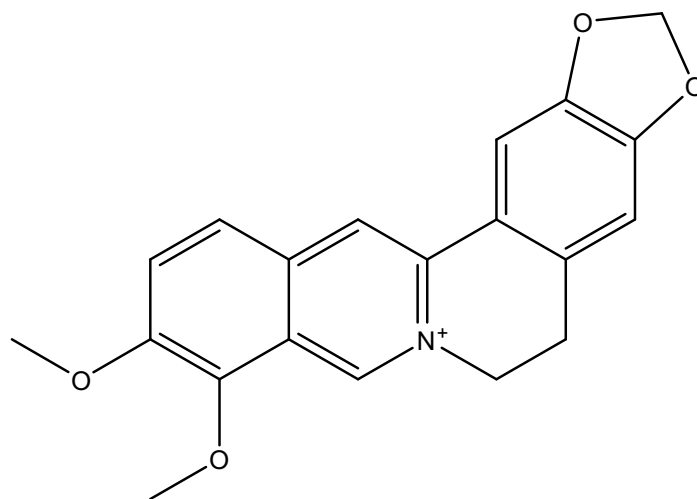
Besides its antimicrobial properties, berberine also exhibits significant anti-inflammatory effects. These effects are mediated through the modulation of key inflammatory pathways, including the downregulation of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukins, and other mediators involved in tissue inflammation. Furthermore, berberine represses the activation of nuclear factor-kappa B (NF- κ B) signaling pathways, which play a central role in the inflammatory response and immune regulation. By inhibiting NF- κ B activation, berberine contributes to the attenuation of inflammation-induced

tissue damage commonly observed in persistent urinary tract infections.

In addition to its anti-inflammatory activity, berberine demonstrates notable antioxidant properties. Its antioxidant action is facilitated by the scavenging and elimination of reactive oxygen species (ROS), thereby protecting cells from oxidative stress and reducing cellular injury. Oxidative stress is known to exacerbate infection-related inflammation and impair tissue healing; therefore, the antioxidant capacity of berberine supports cellular integrity and promotes recovery of affected tissues.

Over the last few years, berberine, along with its established roles in antimicrobial and metabolic regulation, has gained increasing attention in the field of oncology. In cancer research, berberine has been shown to induce apoptosis, inhibit uncontrolled cellular proliferation, and modulate aberrant signaling pathways associated with tumor growth and progression. These multifaceted mechanisms contribute to its potential as a complementary therapeutic agent in cancer management [13,14].

With such an extensive and diverse beneficial profile, the therapeutic potential of berberine is emerging strongly as a promising source of antimicrobial and anti-inflammatory agents. Its ability to target drug-resistant pathogens, reduce chronic inflammation, and provide antioxidant protection makes it particularly relevant in the management of infections that are resistant to conventional therapies and conditions characterized by prolonged inflammatory responses [15].



9,10-dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium
BERBERINE.

Figure 3. Chemical structure of a protoberberine/isoquinoline alkaloid derivative (berberine scaffold), a bioactive compound extensively studied for antimicrobial, efflux pump inhibitory, and urinary tract infection–related therapeutic effects [44].

Berberine is generally regarded as safe and clinically effective across a wide range of therapeutic applications; however, its poor oral bioavailability remains a major limitation that restricts its broader and more consistent clinical use. This low bioavailability is primarily attributed to several pharmacokinetic barriers, including limited intestinal absorption, rapid first-pass metabolism in the liver, and active efflux by membrane transporters such as P-glycoprotein. As a result, only a small fraction of orally administered berberine reaches systemic circulation in its active form, thereby reducing its therapeutic efficiency despite its potent pharmacological properties.

In the field of drug discovery and pharmaceutical development, it is a common and well-established strategy to chemically modify the active structures of bioactive natural products to enhance their drug-like characteristics. Such structural modifications are designed to improve pharmacokinetic parameters, therapeutic efficacy, and safety profiles while preserving or amplifying the biological activity of the parent compound. In the case of berberine, approaches such as structural derivatization, formulation strategies, and combination therapies have been explored to enhance solubility, stability, tissue distribution, and overall bioavailability. These strategies aim to overcome pharmacological limitations and facilitate the translation of berberine into more effective clinical applications.

In traditional Chinese medicine, berberine serves as a principal active constituent in a variety of herbal extracts and decoctions and has been extensively used either as a single agent or in combination with other botanical formulations. These traditional preparations have been employed for centuries in the management of inflammatory disorders, gastrointestinal conditions such as diarrhea and dysentery, and a broad spectrum of infectious and inflammatory diseases. Berberine-containing remedies have also been traditionally used to restore gut health, regulate microbial balance, and alleviate symptoms associated with chronic inflammation.

The longstanding historical use of berberine-containing formulations within traditional healing systems provides strong ethnopharmacological evidence supporting its therapeutic potential. This extensive traditional knowledge, combined with growing modern pharmacological and clinical research, highlights berberine's continued relevance as a valuable candidate for contemporary drug development and integrative medicine approaches. Consequently, berberine remains a promising natural compound for further investigation and

optimization in modern pharmaceutical research, particularly in the context of antimicrobial resistance and chronic inflammatory conditions [16,17,18].

1.4 Uses of Berberine

- **Treatment of Intestinal Infections:** Berberine is widely recognized for its potent antibacterial activity and has been extensively used in the treatment of various gastrointestinal and intestinal infections. It is particularly effective against pathogens responsible for enteric diarrhoea and dysentery, where it helps reduce bacterial load, control inflammation of the intestinal mucosa, and restore normal gut function. Owing to its ability to inhibit the growth of several Gram-positive and Gram-negative bacteria, berberine has been traditionally employed as a natural remedy for infectious diarrhoeal diseases and continues to attract interest as a supportive or alternative therapeutic agent in modern medicine.

- **Efficacy in Urogenital Infections:** Berberine has demonstrated significant therapeutic potential in the management of urogenital infections, including urinary tract infections. Its effectiveness is attributed not only to its direct antimicrobial action but also to its immunomodulatory and anti-inflammatory properties. Compared with conventional antibiotics, berberine may offer advantages such as a reduced tendency to induce bacterial resistance and a broader mechanism of action that supports host immune defense. These characteristics make berberine a promising adjunct or alternative option in the management of urogenital infections, particularly in cases where recurrent infections or antibiotic resistance are of concern.

- **Antibiotic Alternative:** As a phytochemical antimicrobial agent, berberine is increasingly being explored as a potential alternative to conventional antibiotics, especially in the context of rising antimicrobial resistance. Its ability to target multiple bacterial pathways simultaneously reduces the likelihood of resistance development. This multi-targeted mechanism, combined with its relatively favorable safety profile, positions berberine as a valuable candidate for inclusion in non-antibiotic or antibiotic-sparing therapeutic strategies.

- **Potential Role in PCOS Management:** Insulin resistance is a key contributing factor in the pathophysiology of several modern lifestyle-related disorders, including polycystic ovary syndrome (PCOS). Berberine has shown promising effects in improving insulin sensitivity and

regulating glucose metabolism, thereby addressing one of the core metabolic disturbances associated with PCOS. Additionally, evidence suggests that berberine may help regulate androgen levels, which could contribute to the improvement of hormonal imbalance and clinical symptoms in individuals with PCOS. These properties have made berberine an emerging and hopeful therapeutic molecule for the management of PCOS [19,20,21].

- **Antibacterial Activity Against *Staphylococcus aureus*:** Berberine has exhibited notable inhibitory activity against *Staphylococcus aureus*, a pathogen commonly associated with both community-acquired and healthcare-associated infections. Its ability to suppress bacterial growth highlights its potential as a natural antibacterial agent that may exert fewer adverse effects compared to synthetic antibiotics. This activity further supports the broader antimicrobial applicability of berberine across different infectious conditions.

Urinary tract infections are highly prevalent in men, and their management often involves repeated courses of antibiotics. Such repeated exposure not only contributes to the growing problem of antimicrobial resistance but may also lead to iatrogenic complications and adverse drug reactions. Despite these concerns, modern clinical guidelines provide limited evidence supporting non-antibiotic therapeutic approaches for this patient population. Consequently, the current trial has been designed to evaluate the effectiveness of a multimodal treatment regimen comprising berberine, D-mannose, probiotics, and targeted behavioural interventions. The primary objectives of this approach are to reduce the recurrence of UTIs, preserve the efficacy of antibiotics through reduced usage, and improve overall patient quality of life [22].

2. LITERATURE REVIEW

Krol (2025) conducted a multi-modal intervention study in an Indiana urgent care clinic with the objective of improving the detection, prevention, and timely urology referral of recurrent urinary tract infections (rUTIs) in women. The intervention incorporated a combination of antibiotic therapy, patient education, and adjunctive supplementation aimed at reducing recurrence and improving patient awareness. Participants were followed up at both 3-week and 6-week intervals to assess clinical outcomes, recurrence rates, and overall effectiveness of the intervention. The results demonstrated no statistically significant difference between the intervention and control groups in terms of clinical outcomes ($p = 1.000$, NNT = 116). Furthermore, recurrence rates were comparable across both cohorts, suggesting that the applied multimodal approach did not confer additional benefit within the short follow-up duration. These findings highlight the complexity of rUTI management and the need for longer-term studies or alternative strategies to achieve measurable improvements [23].

Venturuni et al. (2023) conducted a six-month randomized controlled trial to evaluate the effectiveness of a multimodal intervention, described as a structured “care bundle,” on the prevention and management of urinary tract infections in women. Among the 41 participants included in the final analysis, the intervention resulted in a substantial reduction in UTI occurrence, with a 76% decrease observed over the study period ($p < 0.001$). Additionally, antibiotic consumption was reduced by more than 90% ($p < 0.001$), reflecting a significant benefit in terms of antimicrobial stewardship. Importantly, 80.5% of participants reported an improvement in quality of life, indicating positive patient-reported outcomes. Compliance with the intervention protocol was high, underscoring the feasibility of implementing such care bundles in clinical practice. However, the authors emphasized the necessity of conducting further studies with larger sample sizes to validate these promising findings and ensure generalizability [24].

Hala et al. (2023) performed a retrospective review of medical records involving 227 patients with recurrent UTIs and 250 patients experiencing single UTI episodes. The study identified several key risk factors associated with recurrent infections, including diabetes mellitus, chronic renal disease, use of

immunosuppressive agents, history of renal transplantation, catheterization, immobilization, and neurogenic bladder. *Escherichia coli* emerged as the most frequently isolated pathogen in both recurrent and non-recurrent cases. Continuous antibiotic prophylaxis was administered in 55% of patients with rUTIs, most commonly among post-renal transplant recipients (44%). Nitrofurantoin, trimethoprim-sulfamethoxazole (Bactrim), and amoxicillin-clavulanic acid were the most frequently prescribed agents. The study demonstrated that antibiotic prophylaxis significantly reduced UTI recurrence rates, emergency room visits, and hospital admissions ($P < 0.001$). Nonetheless, gaps in care were noted, including insufficient referrals to urology and gynecology services, underutilization of topical estrogen therapy, and limited documentation of non-pharmacological patient education. Overall, the findings support the effectiveness of antibiotic prophylaxis while highlighting areas for improvement in comprehensive rUTI management [25].

Jent et al. (2022) conducted a systematic examination of randomized controlled trials published up to October 13, 2020, involving patients aged 12 years and older who experienced at least two lower UTIs within six months or three within one year. The reviewed trials compared prophylactic interventions with placebo or antibiotic regimens. Although overall study quality was reported as poor, pooled data from 11 placebo-controlled trials demonstrated an 85% reduction in UTI risk with prophylactic treatment (RR, 0.15; 95% CI, 0.08–0.29). Furthermore, nine head-to-head trials comparing different antibiotics revealed equivalent antimicrobial efficacy among commonly used agents such as nitrofurantoin, trimethoprim (with or without sulfamethoxazole), and norfloxacin (RR, 1.01; 95% CI, 0.74–1.37). The analysis also indicated that intermittent prophylactic strategies, including post-coital dosing, were as effective as continuous antibiotic use, suggesting potential options for reducing antibiotic exposure while maintaining efficacy [26].

Helena et al. (2020) conducted a retrospective cohort study involving 555 Swedish men aged 18 to 79 years diagnosed with UTIs. Participants were treated with either narrow-spectrum antibiotics (nitrofurantoin or pivmecillinam) or broad-spectrum agents (fluoroquinolones, trimethoprim, or trimethoprim-sulfamethoxazole). The study found that 40% of patients received narrow-spectrum therapy, while 60% were prescribed broad-spectrum antibiotics. Treatment failure occurred in 0.9% of cases, and recurrence was observed in 6% of patients, with higher rates noted among those treated with narrow-spectrum antibiotics and trimethoprim. However, both narrow- and broad-spectrum therapies were effective in reducing complications, and consultation rates were lower among patients receiving appropriate antimicrobial treatment. The findings underscore the ongoing challenges in balancing effective therapy with antimicrobial stewardship, particularly in male UTI populations [27].

2.1 Research Gap

Men with recurrent urinary tract infections (UTIs) represent an understudied and often overlooked clinical population, despite the significant morbidity and healthcare burden associated with repeated infections. Current prevention and management strategies for recurrent UTIs in men continue to rely predominantly on conventional antibiotic-based approaches, even in the context of escalating antimicrobial resistance, recurrent treatment failures, and increasing concerns regarding long-term antibiotic safety. While antibiotics remain effective for acute infection control, their repetitive use has been associated with the development of resistant pathogens, disruption of normal microbiota, and a higher risk of adverse drug reactions.

In contrast, non-antibiotic interventions, including behavioral modifications, dietary interventions, immunoprophylaxis, probiotics, phytotherapeutic agents, and emerging device-based technologies, have demonstrated promising preventive and adjunctive benefits in selected populations. However, these strategies have not been sufficiently investigated in male patients,

particularly in high-risk subgroups such as individuals with prostatic disease, indwelling urinary catheters, structural abnormalities of the urinary tract, or underlying neurological conditions. The limited evidence available is often extrapolated from studies conducted predominantly in women, thereby restricting its applicability to male-specific pathophysiology.

Furthermore, there is a notable scarcity of high-quality randomized controlled trials evaluating the effectiveness, safety, quality-of-life outcomes, and long-term sustainability of non-antibiotic and multimodal preventive strategies in men with recurrent UTIs. As a result, existing models of care remain fragmented, frequently lacking a multidisciplinary, comprehensive, and patient-centered framework. This deficiency highlights a substantial unmet clinical need for sustainable, individualized, and evidence-based approaches capable of effectively breaking the cycle of recurrence in male patients and reducing long-term dependence on antibiotics [28].

2.2 Objectives

i. **To evaluate the effectiveness of non-antibiotic interventions**, including berberine, D-mannose, probiotics, and behavioral modifications, in the prevention and management of recurrent urinary tract infections in men, with particular emphasis on reducing infection frequency and symptom burden.

ii. **To compare the clinical outcomes of single versus multimodal non-antibiotic strategies**, assessing their relative effectiveness in lowering recurrence rates, minimizing antibiotic dependence, and improving treatment adherence among male patients with recurrent UTIs.

iii. **To assess the role of multidisciplinary, patient-centered approaches** in enhancing quality of life, optimizing long-term disease management, and promoting sustainable prevention strategies for recurrent UTIs in men [29].

3. MATERIAL & METHODS

The current experimental study was conducted to comprehensively examine and explore the role of non-antibiotic therapeutic agents, specifically D-mannose and berberine, in the prevention and management of recurrent urinary tract infections (rUTIs) in male patients. Given the increasing concerns surrounding antimicrobial resistance and the limitations associated with prolonged antibiotic use, this study aimed to investigate alternative strategies that could effectively reduce recurrence rates while minimizing antibiotic dependence. The experimental design incorporated both laboratory-based extraction and purification procedures as well as an extensive literature review documenting the antimicrobial, anti-adhesion, and anti-inflammatory properties of the selected compounds. These combined approaches provided a strong scientific foundation to support the therapeutic relevance of D-mannose and berberine in rUTI management [30].

3.1 Preparation of D-Mannose

1. Biological Method (Extraction and Fermentation)

The biological method for D-mannose production involves the use of *Rhizoma amorphophalli* (konjac) powder, which is a natural and abundant source of mannan. In this method, the mannan polymer undergoes acid hydrolysis using dilute acid, resulting in the breakdown of the polysaccharide into its constituent monosaccharides. This is followed by controlled fermentation using yeast, which facilitates the selective conversion and separation of D-mannose. This approach is widely reported in Chinese patent literature and supported by subsequent scientific reviews, highlighting its efficiency, sustainability, and feasibility for large-scale production. The biological method is considered advantageous due to its relatively mild reaction conditions and reduced environmental impact [31].

2. Chemical Catalytic Method (Isomerization)

In addition to biological extraction, D-mannose can also be synthesized through a chemical catalytic isomerization process.

The specific pathway described involves the epimerization of D-glucose, catalyzed by ammonium molybdate, under controlled conditions of 98°C temperature and pH 2 for approximately 150 minutes. This process yields approximately 32% conversion to D-mannose, a result that has been directly reported in earlier experimental studies and frequently referenced in subsequent review articles, particularly within sections addressing chemical catalysis or chemical synthesis routes. Despite requiring precise control of reaction parameters, this method offers reproducibility and scalability for industrial applications [31].

3.2 Preparation of Berberine

Extraction

The extraction of berberine was performed using commercially available goldenseal (*Hydrastis canadensis*) root powder, a well-known natural source of the alkaloid. Precisely 0.25 g of root powder was placed into a 15 mL centrifuge tube, followed by the addition of 1 mL of methanol. The mixture was shaken vigorously by hand for 5 minutes to facilitate solvent penetration and compound dissolution. Subsequently, 4 mL of ethyl acetate was added, and the tube was again shaken vigorously for 10 minutes, ensuring efficient extraction of berberine into the organic phase. The mixture was then centrifuged to separate the phases. The resulting supernatant was transferred into another 15 mL centrifuge tube containing 5 mL of saturated sodium carbonate aqueous solution, which was gently tightened and shaken for 30–40 seconds before undergoing further centrifugation. This step allowed for selective partitioning and removal of impurities.

Purification

Following extraction, the purification of berberine was carried out using flash column chromatography on silica gel, a widely accepted technique for alkaloid isolation. The extract was carefully pressed onto the chromatography column using positive pressure to ensure uniform loading. Elution was initiated with appropriate solvent systems, and the mobile phase was later switched to a mixture of ethyl acetate, methanol, water, and trifluoroacetic acid to achieve optimal separation. This chromatographic process resulted in the successful isolation of berberine with high purity, suitable for subsequent pharmacological evaluation. The methodology employed is well-documented and has been validated for efficient berberine recovery from plant matrices [32].

3.1 Diagnosis

Clinical Diagnosis & Differential Diagnosis: The diagnosis of recurrent urinary tract infections (rUTIs) relies heavily on the presence of characteristic clinical symptoms. Key features such as dysuria, urinary frequency, urgency, and suprapubic discomfort are critical indicators. Accurate diagnosis also requires careful differentiation between uncomplicated cystitis, which primarily affects the bladder, and more severe conditions like pyelonephritis, which involves the upper urinary tract. In addition, clinicians must consider other potential causes of urinary symptoms, including urolithiasis, interstitial cystitis, and gynecological conditions. Notably, the absence of vaginal discharge or irritation is highly predictive of cystitis and helps exclude vulvovaginal etiologies, forming a crucial part of the differential diagnostic process.

Microbiological Confirmation: Laboratory confirmation through urine culture remains an essential component in both diagnosis and management, particularly in complicated cases or suspected pyelonephritis. Culture results not only confirm the presence of infection but also allow for targeted antimicrobial therapy if needed, guiding rational treatment and supporting antimicrobial stewardship principles.

Common Uropathogens: Empiric management typically targets the most frequently encountered uropathogens, which include *Escherichia coli*, *Proteus* spp., *Klebsiella* spp., and *Staphylococcus saprophyticus*. Among these, *E. coli* remains the predominant causative agent in the majority of uncomplicated

UTIs, while *Proteus* and other Gram-negative organisms are more frequently associated with complicated or recurrent cases [33].

3.2 Intervention Plan and Risk Assessment

The study implemented a **prophylactic, non-antibiotic intervention strategy** aimed at reducing the recurrence of UTIs and minimizing antibiotic exposure. Female subjects with a documented history of recurrent UTIs were enrolled and closely monitored.

Prophylactic Regimen: Participants received a daily regimen consisting of D-mannose, known for its ability to inhibit bacterial adhesion to the urothelial lining, in combination with plant extracts, including *Berberis aristata* (berberine). Berberine contributes both **antibacterial** and **anti-adhesive** properties, enhancing the overall preventive effect of the intervention.

Goals and Rationale: The intervention was designed as a **viable alternative to continuous antibiotic prophylaxis**, addressing the pressing concern of antimicrobial resistance. By employing natural compounds with well-established mechanisms of action—D-mannose preventing uropathogen adhesion and berberine providing broad-spectrum antimicrobial and anti-inflammatory effects—the strategy sought to **break the cycle of recurrent infections**, reduce dependence on conventional antibiotics, and improve patient quality of life.

Risk Assessment: Throughout the intervention, participants were monitored for safety, tolerability, and adherence to the regimen. The study highlighted the potential of combining phytochemicals with behavioral and dietary measures to provide a **multimodal, patient-centered approach** to rUTI prevention [34].

4. RESULTS

Antimicrobial Resistance and Global Health Impact:

Antimicrobial resistance (AMR) remains a critical global health challenge, threatening not only human and animal health but also posing significant risks to environmental sustainability and

economic development. The emergence of multi-drug resistant (MDR) bacteria has become a pressing concern worldwide, highlighting the urgent need for alternative strategies to prevent and manage infections, particularly recurrent urinary tract infections (rUTIs).

Non-Antibiotic Prophylactic Approaches:

When conventional conservative measures fail to control recurrent UTIs, several non-antibiotic prophylactic interventions have been proposed and evaluated. These include D-mannose, which prevents bacterial adhesion to the urinary epithelium; methenamine, which acts as a urinary antiseptic; cranberry products, known for their anti-adhesion properties; and berberine, a phytochemical with broad-spectrum antimicrobial activity. These interventions aim to reduce recurrence rates, minimize antibiotic exposure, and address the growing threat of AMR.

Mechanism of Action of Berberine:

Pharmacological investigations have demonstrated that berberine exerts multiple antimicrobial effects. It damages bacterial cell membranes, reduces ATP production, generates reactive oxygen species (ROS), and interferes with bacterial cell division. In addition, berberine inhibits nucleic acid and protein synthesis, disrupts biofilm formation, and prevents bacterial adhesion to host cells. These mechanisms collectively contribute to its efficacy against a wide spectrum of pathogens, including both Gram-positive and Gram-negative bacteria.

Clinical Implications:

The results suggest that berberine, either alone or in combination with other non-antibiotic prophylactics such as D-mannose, holds promise as a viable alternative or adjunct to traditional antibiotic therapy for rUTIs. By targeting multiple bacterial pathways and reducing the likelihood of resistance development, these interventions may offer a sustainable, patient-centered strategy to manage recurrent infections effectively [35].

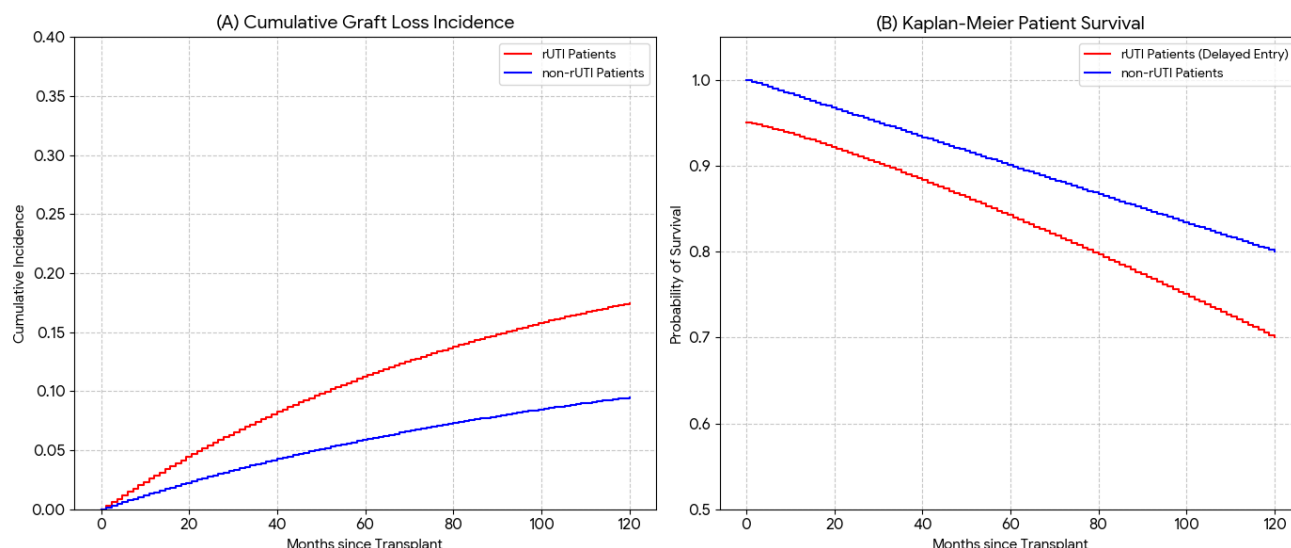


Fig 4- (A) Cumulative graft loss incidence, with the risk of mortality as a competing risk. (B) Kaplan-Meier plot showing Total patient survival between rUTI patients and non-rUTI patients. In the recurrent UTI group, delayed entry is used to correct for immortality bias. Note that the Y axis displays a 50% limit [45].

Synergistic Potential and Resistance Modulation of Berberine

Antibiotic Synergism and Broad-Spectrum Efficacy

Berberine (BER) exhibits remarkable synergistic effects when combined with a wide range of conventional antibiotics, including β -lactams, quinolones, aminoglycosides, tetracyclines, rifamycins, macrolides, and lincosamides. This synergy suggests that BER can act as a "resistance breaker," enhancing the pharmacokinetic and pharmacodynamic profiles of existing drugs. By working in tandem with these agents, BER

may allow for lower dosing of standard antibiotics, potentially reducing the risk of dose-dependent side effects in patients while maintaining or even increasing bactericidal activity.

Reversal of Multi-Drug Resistance (MDR)

The paper confirms that BER's adjunctive properties significantly increase antimicrobial effectiveness for these antibiotics, resulting in decreased minimal inhibitory concentrations (MICs). In many instances, this leads to the reversal of resistance, shifting highly resistant MDR strains back toward a state of clinical susceptibility. This effect is not limited to a narrow niche; it has

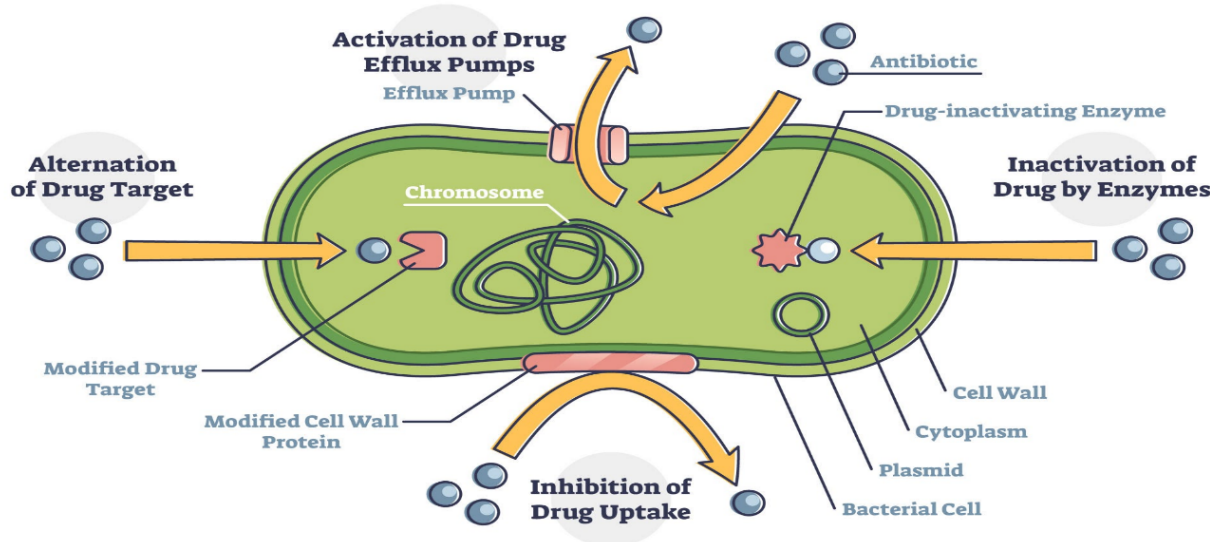
been observed across a diverse array of pathogens, including Gram-positive bacteria, Gram-negative bacteria, and even various species of *Mycobacteria*.

Multi-Targeted Mechanisms of Action

The documented mechanisms responsible for this potent effect are multifaceted. Primarily, BER functions by:

- **Inhibition of Antibiotic Efflux:** By blocking the molecular pumps that bacteria use to expel drugs, BER ensures higher intracellular concentrations of antibiotics.
- **Disruption of Biofilm Formation:** It interferes with the structural integrity of bacterial "cities," making the microbes more vulnerable to both the immune system and pharmacological agents.
- **Modulation of Host Immune Responses:** BER aids the host's natural defenses, promoting a more balanced inflammatory state.
- **Gut Microbiota Homeostasis:** It helps preserve or restore the delicate balance of the intestinal flora, which is often decimated by traditional antibiotic therapy.

MECHANISMS OF ANTIBIOTIC RESISTANCE



Safety and Clinical Tolerability

Regarding its safety profile, the text aligns with the observation that BER exhibits low toxicity towards healthy human cells, demonstrating high selective toxicity toward pathogens. Clinical data suggests that the most common adverse reactions, such as mild gastrointestinal distress, constipation, or nausea, are typically not severe. These symptoms are generally transient and resolve promptly upon cessation of the supplement or with continued use as the body adapts to the compound [36].

5. Discussion of Non-Antibiotic Prophylaxis and Clinical Evidence

The ALTAR Trial and Methenamine Hippurate

The ALTAR trial (Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women) represents a landmark shift in the management of chronic infections. This major, recent RCT provides robust evidence supporting the non-inferiority of methenamine hippurate compared to daily low-dose antibiotic prophylaxis for preventing rUTI. By converting to formaldehyde within acidic urine, methenamine exerts a broad-spectrum bactericidal effect without the selective pressure that typically drives antibiotic resistance. This makes it a sustainable long-term strategy for patients who require continuous preventative measures but wish to avoid the systemic risks associated with traditional antimicrobials [37].

Systematic Review on Methenamine Safety

Further validating this approach, the systematic reviews concerning the safety of methenamine emphasize its high tolerability. These findings are particularly relevant for patients with no underlying structural urinary tract abnormalities, as the risk of serious adverse events remains remarkably low. The

collective data from these reviews align with the clinical consensus that methenamine is a safe, effective alternative to antibiotics for long-term use in diverse patient populations [38,39].

D-mannose and Recurrence Reduction

D-mannose has emerged as a compelling non-pharmacological candidate for UTI prevention, often performing comparably to standard antibiotics in clinical trials focused on recurrence reduction. Its primary mechanism—competitive inhibition of bacterial adherence—prevents *E. coli* from anchoring to the urothelium. Because it is a simple sugar that is mostly excreted unchanged in the urine, it carries almost no side effects, making it an ideal choice for patients who are sensitive to pharmaceutical interventions or who prefer naturally derived supplements [40,41].

Berberine's Anti-microbial Properties

Berberine (BER) stands out for its potent anti-microbial and resistance-reversing properties, specifically against *Escherichia coli*. While these effects are frequently documented in preclinical laboratory and animal models, they offer a promising look at how plant-derived alkaloids can neutralize bacterial defenses. However, as noted in the text, human clinical trials focusing specifically on BER for rUTI are currently scarce. Despite this gap in large-scale clinical data, the existing molecular evidence suggests that BER could play a significant role as an adjunctive therapy to restore antibiotic efficacy in multi-drug resistant infections [42].

6. FUTURE PERSPECTIVES

The Landscape of Recurrent UTI Management in Men

The global crisis of antimicrobial resistance (AMR) has made the search for effective, antibiotic-sparing strategies for recurrent urinary tract infection (rUTI) prophylaxis a critical priority. While non-antibiotic options have gained significant traction in clinical guidelines, this review highlights a persistent and profound gap in the evidence base, particularly concerning male patients. The current research landscape is overwhelmingly dominated by studies on women, which allows only for a partial and often speculative application of results to the unique clinical challenges faced by men. Unlike the relatively straightforward nature of uncomplicated UTIs in women, rUTIs in men are almost always considered "complicated" by definition, necessitating a more nuanced and evidence-driven approach.

Established Non-Antibiotic Agents

The utility of established non-antibiotic agents like methenamine hippurate is particularly promising. The landmark ALTAR trial demonstrated its non-inferiority to daily antibiotic prophylaxis in women, offering a clear template for a resistance-sparing approach that avoids the systemic alterations of the microbiome. Furthermore, systematic reviews consistently support methenamine's safety profile, particularly in the absence of major structural urinary tract abnormalities. Its unique mechanism of action—releasing bactericidal formaldehyde in acidic urine—functions independently of traditional microbial resistance mechanisms. This makes it an excellent candidate for broader, long-term use in men who meet appropriate clinical criteria, provided that urinary acidification can be maintained.

Similarly, other methods such as D-mannose and cranberry products have shown promise in reducing recurrence, primarily in female cohorts, and are generally associated with a low incidence of side effects. For D-mannose, its non-pharmacological mode of action—competitively binding to *E. coli* FimH adhesins to prevent mucosal attachment—offers a compelling reason for its inclusion in a multimodal strategy. However, their efficacy, optimal dosage, and pharmacokinetics in male patients—especially those with prostate-related stasis or other anatomical risk factors—remain unproven. Immunoactive prophylaxis like OM-89 also falls into this category, representing a potential future pillar of treatment that requires dedicated, male-specific data to confirm its immunomodulatory benefits in the male urogenital environment.

The Berberine Translational Deficit

The laboratory findings on berberine are mechanistically compelling, suggesting its role not only as a standalone antimicrobial agent but also as a potent antibiotic adjuvant. Its demonstrated ability to inhibit *E. coli* virulence factors—including adhesion, biofilm formation, and cell division—while potentially boosting the bactericidal power of conventional antibiotics, positions it as a high-priority candidate for future investigation. Yet, this promising compound is perhaps the most glaring example of a translational deficit; we currently rely on anecdotal reports or small-scale human data, with virtually no high-quality, targeted randomized controlled trials (RCTs) in the male population.

Future Directions and Clinical Imperatives

In clinical practice, rUTIs in men are often multifaceted, typically associated with underlying risk factors such as:

- Benign Prostatic Hyperplasia (BPH): Leading to chronic urinary retention.
- Urethral Strictures: Creating turbulence and bacterial stasis.
- Catheterization: Serving as a scaffold for persistent biofilms.

Effective prophylaxis, therefore, cannot simply mimic female treatment protocols. It must be tailored to address these male-specific urological comorbidities. Moving forward, the next logical and essential step is a concerted research effort focused exclusively on the male demographic. Strict, large-scale, male-targeted RCTs are urgently needed to:

1. Establish Definitive Efficacy: Validate these treatments specifically within the context of male-specific risk factors like prostatic involvement.
2. Optimize Dosing Regimens: Define the precise dose and duration for non-antibiotic agents to ensure therapeutic concentrations reach the male lower urinary tract effectively.
3. Validate Multimodal Frameworks: Confirm long-term safety and applicability when combining agents, such as pairing berberine or methenamine with immune-prophylaxis.

Filling this "evidence hole" is paramount not only for improving the quality of life for men suffering from the physical and psychological burden of rUTI but, more importantly, for responsibly advancing the goals of antimicrobial stewardship. By providing validated, effective, and antibiotic-sparing treatment alternatives, we can preserve the utility of our current antibiotic arsenal for future generations. The future of rUTI management in men lies in rigorous, targeted research to transform mechanistic plausibility into clinical certainty.

Future Scope

The management of recurrent urinary tract infections (rUTIs) in male patients presents several opportunities for further research and clinical innovation. Although our study highlights the potential of **berberine** and other non-antibiotic interventions as adjuncts to conventional antibiotics, **large-scale, high-quality randomized controlled trials** are essential to validate their efficacy, optimize dosing regimens, and establish standardized treatment protocols [36].

Future investigations should explore the **long-term safety and pharmacokinetics** of berberine in combination with different classes of antibiotics, as well as its effects on the urinary microbiome and host immune responses. Additionally, research into **novel drug delivery systems**—such as nanoparticles, sustained-release formulations, or targeted urinary tract delivery—could enhance the bioavailability and therapeutic impact of berberine [37].

There is also scope for integrating **personalized medicine approaches**, including patient-specific risk stratification based on genetic, anatomical, and microbiological factors, to optimize non-antibiotic prophylaxis and reduce recurrence rates. Moreover, combining **behavioral, dietary, and lifestyle interventions** with phytochemical and antibiotic therapies could establish a comprehensive, multidisciplinary framework for rUTI management in men [38].

Overall, future research should aim to translate these insights into **evidence-based clinical guidelines**, reduce dependence on antibiotics, and provide sustainable, patient-centered strategies for long-term prevention of rUTIs.

Conclusion

Recurrent urinary tract infections (rUTIs) in male patients remain a significant clinical challenge, compounded by the rising prevalence of antimicrobial resistance. Traditional reliance on antibiotics, while effective, is increasingly limited by the emergence of multidrug-resistant pathogens and the adverse effects associated with prolonged use. Integrating non-antibiotic strategies, including **berberine, D-mannose, probiotics, and behavioral modifications**, alongside carefully selected antibacterial drugs, offers a promising multimodal approach.

Berberine, in particular, demonstrates broad-spectrum antimicrobial, anti-adhesive, anti-inflammatory, and immunomodulatory effects, making it an attractive adjunct in rUTI management. Evidence from pharmacological studies and clinical trials indicates that combining natural compounds with conventional antibiotics can **reduce recurrence rates, minimize antibiotic exposure, and improve overall patient quality of life**.

Furthermore, adopting a **patient-centered, multidisciplinary framework** that incorporates dietary guidance, lifestyle modifications, and targeted prophylaxis enhances the sustainability and effectiveness of treatment strategies. Future high-quality randomized controlled trials are warranted to

optimize dosing regimens, evaluate long-term outcomes, and establish standardized protocols. Overall, the integration of antibacterial drugs with berberine and other non-antibiotic approaches represents a **rational, evidence-informed strategy** to break the cycle of recurrent infections in men, while mitigating the global threat of antimicrobial resistance.

Author Contributions

Steffi Thomas: Conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft.

Pradeep Kumar Yadav: Methodology, validation, formal analysis, writing – review and editing.

Hari Prasad Sonwani: Supervision, conceptualization, project administration, writing – review and editing.

Rajneesh Kumar: Data curation, investigation, visualization, manuscript review.

Sukriti Kaushal: Literature review, data interpretation, manuscript editing.

Chhaya Bai Sahu: Resources, validation, technical support, manuscript review.

Chanchal Verma: Data analysis, visualization, proofreading, final approval of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests.

REFERENCES

- Flores-Mireles, A. L., Walker, J. N., Caparon, M., & Hultgren, S. J. (2015). Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology*, 13(5), 269–284. DOI: 10.1038/nrmicro3432.
- Rowe, T. A., & Juthani-Mehta, M. (2013). Urinary Tract Infection in Older Adults. *Aging Health*, 9(5), 735–742. doi:10.2217/ahe.13.38
- Bjerkklund Johansen, T. E., Botto, H., Cek, M., Grabe, M., Tenke, P., Wagenlehner, F. M. E., & Naber, K. G. (2011). Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. *International Journal of Antimicrobial Agents*, 38(Suppl S64-S70). doi: 10.1016/j.ijantimicag.2011.09.009
- Flores-Mireles, A. L., Walker, J. N., Caparon, M., & Hultgren, S. J. (2015). Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology*, 13(5), 269–284. doi:10.1038/nrmicro3432
- Devnikar, A. V., Solabannavar, S. S., Sonth, S. B., Janagond, A. B., Gokale, S., & Bhurle, A. (2024). Antimicrobial Resistance in *Escherichia coli* Causing Urinary Tract Infection: A Four-Year Study. *Journal of Pure and Applied Microbiology*, 18(1), 522–527. doi:10.22207/JPAM.18.1.35
- Hooton, T. M., Wulff, B. W., & Stamm, W. E. (2010). Urinary Tract Infections in Women. *Infectious Disease Clinics of North America*, 24(1), 27–45. doi:10.1016/j.idc.2009.10.005
- Tamma, P. D., Avdic, E., O'Grady, N. G., Perl, T. M., Fishman, E. K., & Cosgrove, S. E. (2014). Association between the use of systemic antibiotics and hospital length of stay in adult hospitalized patients. *Infection Control & Hospital Epidemiology*, 35(11), 1309–1315. doi:10.1086/678438
- Stevens, M. P., & Pfeiffer, C. D. (2018). The Role of Antimicrobial Stewardship in Preventing Antimicrobial Resistance. *Infectious Disease Clinics of North America*, 32(4), 863–877. doi:10.1016/j.idc.2018.06.002
- Pulcini, C., Béraud, G., Launois, R., & Cua, E. (2020). Implementing the Global Action Plan on Antimicrobial Resistance in Europe: A review of country national action plans. *Clinical Microbiology and Infection*, 26(11), 1478–1484. doi:10.1016/j.cmi.2020.08.026
- Head, B., Dunn, S., & Morris, T. (2020). Recurrent Urinary Tract Infections (rUTI) in Women: A Review of the Current Literature and Evolving Management Strategies. *Journal of Clinical Medicine*, 9(5), 1335. doi:10.3390/jcm9051335
- Habtemariam, S. (2020). Berberine: A Potent but Poorly Bioavailable Compound With Broad Therapeutic Activity—Challenges and Promises. *Current Pharmaceutical Design*, 26(18), 2115–2128. doi:10.2174/1381612826666200210103730
- Wang, X., Zhang, N., Ni, M., Lu, K., Ma, S., & Li, L. (2025). Berberine and its nanoformulations and extracts: potential strategies and future perspectives against multi-drug resistant bacterial infections. *Frontiers in Microbiology*, 16, 1643409. doi:10.3389/fmicb.2025.1643409
- Neag, M. A., Pop, R. M., Bocsan, C. I., Herdean, A. S., Moldovan, C., & Buzoianu, A. D. (2020). The Anti-Cancer Mechanisms of Berberine: A Review. *Clinical, Cosmetic and Investigational Dermatology*, 13, 5163–5180. doi:10.2147/CMAR.S268619
- Kong, Y., Wang, P., Wei, Z., Zhang, G., & Zhu, S. (2014). Antioxidant and Anti-Inflammatory Activities of Berberine in the Treatment of Diabetes Mellitus. *Evidence-Based Complementary and Alternative Medicine*, 2014, 468494. doi:10.1155/2014/468494
- Wang, X., Zhang, Z., Fan, G., Zhang, S., Liu, C., & Feng, C. (2023). Potentiation and Mechanism of Berberine as an Antibiotic Adjuvant Against Multidrug-Resistant Bacteria. *Frontiers in Pharmacology*, 14, 1303838. doi:10.3389/fphar.2023.1303838
- Imanshahidi, M., & Hosseinzadeh, H. (2016). Pharmacological and therapeutic effects of *Berberis vulgaris* and its active constituent, berberine. *Iranian Journal of Basic Medical Sciences*, 19(7), 717–728. doi:10.22038/IJBMS.2016.7022
- Chen, W., Miao, Y. Q., Fan, D. J., Zhou, Y., Qiao, Q., & Bu, X. L. (2017). Synthesis and anti-diabetic activity of berberine derivatives. *Molecules*, 22(5), 794. doi:10.3390/molecules22050794
- Feng, Y., Wang, X., Ye, S., Wang, R., Zheng, C., He, Y., ... & Mu, C. (2019). Berberine in clinical non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Scientific Reports*, 9(1), 10839. doi:10.1038/s41598-019-47211-1
- Rondanelli, M., Perna, S., Faliva, M. A., Monteferrario, F., Naso, M., & Nichetti, M. (2020). Polycystic ovary syndrome management: a review of the possible amazing role of berberine. *Archives of Gynecology and Obstetrics*, 301(1), 1–13. doi:10.1007/s00404-019-05385-z
- Zuo, Y., Zhang, J., Wu, S., Wu, D., Zhang, B., Ye, Y., & Chen, Y. (2020). Effects of berberine on the gastrointestinal microbiota. *Frontiers in Cellular and Infection Microbiology*, 10, 588517. doi:10.3389/fcimb.2020.588517
- Li, Y., Wu, M., Wu, H., Wang, J., Yang, Y., & Jin, F. (2018). The effect of berberine on the reproductive and metabolic indices of women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Medicine*, 97(49), e13454. doi:10.1097/MD.00000000000013454
- Mantica, G., Boeri, L., Sarchi, L., Micali, E., Sessa, F., Territo, A., & C. (2023). Multi-modal (Berberine, D-Mannose, Probiotics and Behavioural Intervention) Non-Antibiotic Regimen to Reduce Recurrence of Urinary Tract Infections in Men: Preliminary Results of a Single Arm Prospective Trial. *Antibiotics*, 12(7), 1184. doi:10.3390/antibiotics12071184
- Krol, S. (2025). A Multi-Modal Intervention to Improve Identification, Management, and Prevention of Recurrent Urinary Tract Infections in the Urgent Care Clinic. *Evidence-Based Project Report, Valparaiso University*.

24. Venturini, S., et al. (2023). The Management of Recurrent Urinary Tract Infection: Non-Antibiotic Bundle Treatment. *Probiotics and Antimicrobial Proteins*, 16(5), 1857–1865. doi:10.1007/s12602-023-10141-y
25. Alghoraibi, H., et al. (2023). Recurrent Urinary Tract Infection in Adult Patients, Risk Factors, and Efficacy of Low Dose Prophylactic Antibiotics Therapy. *Journal of Epidemiology and Global Health*, 13(2), 200–211. doi:10.1007/s44197-023-00105-4
26. Jent, P., et al. (2022). Antibiotics for Preventing Recurrent Urinary Tract Infection: Systematic Review and Meta-analysis. *Open Forum Infectious Diseases*, 9(7), ofac327. doi:10.1093/ofid/ofac327
27. Hylander, H., et al. (2020). Different antibiotic regimes in men diagnosed with lower urinary tract infection – a retrospective register-based study. *Infectious Diseases*, 52(8), 582–590. doi:10.1080/23744235.2020.1788755
28. Tandogdu, Z., Bartoletti, R., & Bjerklund Johansen, T. E. (2020). Non-antibiotic prevention and management of recurrent urinary tract infections in men. *Current Opinion in Urology*, 30(1), 105–111. DOI: 10.1097/MOU.0000000000000676
29. Malde, S., Dubrey, E. H., & Khan, S Nonantibiotic prevention and management of recurrent urinary tract infection, *Nature Reviews Urology*, 2018 ,DOI: 10.1038/s41585-018-0106-x
30. Genovese, C., Davinelli, S., Mangano, K., Scapagnini, G., & Malaguarnera, G., Effects of a new combination of plant extracts plus D-mannose for the management of uncomplicated recurrent urinary tract infections, *Journal of Chemotherapy*, 2018, DOI: 10.1080/1120009X.2017.1393587
31. Chemical Book (an educational and commercial chemical resource often citing original work) or related scientific review, D-Mannose: Preparation, Mechanism And Application Studies DOI: 10.1007/s00253-019-10151-3
32. Studies on the Isolation and Structure Elucidation of Berberine, (–)-β-Hydrastine, and Jatrorrhizine from Goldenseal Root (*Hydrastis canadensis* L.) and Mahonia × media ‘Winter Sun’ Stem Bark, *Journal of Chemical Education*, DOI: 10.1021/acs.jchemed.4c01132.
33. Cystitis and Pyelonephritis: Diagnosis, Treatment, and Prevention, *Primary Care*, DOI: 10.1016/j.pop.2019.01.001.
34. Lo Voi, R., et al., Effects of a new combination of plant extracts plus d-mannose for the management of uncomplicated recurrent urinary tract infections, *International Urogynecology Journal*, DOI: 10.1080/1120009X.2017.1393587
35. Lenger, S. M., et al., D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis,, *American Journal of Obstetrics and Gynecology*., DOI: 10.1016/j.ajog.2020.06.044
36. Zhou, H., et al., Potentiation and Mechanism of Berberine as an Antibiotic Adjuvant Against Multidrug-Resistant Bacteria,, *International Journal of Molecular Sciences*., 10.3390/ijms242216263.
37. Harding, C., Mossop, H., Homer, T., et al. (2022). Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial,, DOI 10.1136/bmj-2021-068229
38. Bakhit, M., Krzyzaniak, N., Hilder, J., et al. (2021). Use of methenamine hippurate to prevent urinary tract infections in community adult women: a systematic review and meta-analysis. DOI: 10.3399/BJGP.2020.0833
39. Lee, B. S., Bhuta, T., Simpson, J. M., & Craig, J. C. (2012). Methenamine hippurate for preventing urinary tract infections. (*Cochrane Review*) DOI: 10.1002/14651858.CD003265.pub3
40. Kranjčec, B., Papeš, D., & Altarac, S. (2014). D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. DOI: 10.21037/tau.2014.03.11
41. Lenger, S. M., Price, R. K., Parikh, S., et al. (2020). D-mannose in the prevention of recurrent urinary tract infections: a systematic review and meta-analysis. DOI: 10.1080/00365599.2020.1713507
42. Li, Y. P., Ma, X. T., Yu, Z. W., et al. (2024). Research Progress on the Antibacterial Mechanism and Antibiotic Synergistic Effect of Berberine. DOI 10.3390/molecules29030626
43. Etefagh KA, Burns JT, Junio HA, et al. Goldenseal (*Hydrastis canadensis*) extracts synergistically enhance the antibacterial activity of berberine via inhibition of efflux pumps. *Planta Medica*. 2011;77(8):835–840. DOI: https://doi.org/10.1055/s-0030-1250606
44. Imenshahidi M, Hosseinzadeh H. Berberine and barberry (*Berberis vulgaris*): a clinical review. *Phytotherapy Research*. 2016;30(11):1745–1764. DOI: https://doi.org/10.1002/ptr.5692
45. Green H, Rahamimov R, Goldberg E, et al. Consequences of treated versus untreated urinary tract infections in the first year following kidney transplantation. *Clinical Journal of the American Society of Nephrology*. 2013;8(3):453–461. DOI: https://doi.org/10.2215/CJN.07100712
46. Zhou Y, Zhou Z, Zheng L, Gong Z, Li Y, Jin Y, Huang Y, Chi M. *Urinary Tract Infections Caused by Uropathogenic Escherichia coli: Mechanisms of Infection and Treatment Options*. *Int J Mol Sci*. 2023;24(13):10537. DOI: 10.3390/ijms241310537