Phytoconstituents with Anti-Biofilm and Anti-Inflammatory Activities in the Management of Urinary Tract Infection

Bridging Antimicrobial Resistance Through Natural Therapeutics

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Abstract— **Urinary tract infections (UTIs) continue to present significant health and economic concerns, particularly in cases involving recurrent or chronic infections. Conventional antibiotic therapy is often compromised by increasing antimicrobial resistance and the capacity of uropathogens to form biofilms on uroepithelial surfaces and indwelling medical devices. Phytoconstituents derived from medicinal plants are being explored as potential agents with anti-biofilm and anti-inflammatory properties that may influence the management of UTIs through multiple biological mechanisms. Compounds such as flavonoids, terpenoids, phenolic acids, alkaloids, and tannins have been examined for their ability to interfere with quorum sensing, reduce bacterial adhesion, and modulate host inflammatory responses. These activities could potentially alter the course of infection or complement existing therapeutic strategies.**

Experimental investigations have suggested that despite their therapeutic potential, many phytochemicals face limitations related to solubility, stability, and bioavailability. Nanotechnology-based delivery platforms are being considered to address these limitations. Nanoemulsions, liposomes, polymeric nanoparticles, and solid lipid nanoparticles are among the formulations being studied for targeted delivery, sustained release, and improved mucosal penetration. Such systems may also provide opportunities for co-delivery of multiple bioactive agents or combinations with conventional drugs.

Recent research trends indicate an interest in integrating phytoconstituents with nanoformulation strategies to examine their impact on biofilm disruption, inflammatory modulation, and pathogen viability in the context of UTIs. Hypothetical models propose that optimized nanocarrier systems could influence pharmacokinetics and biodistribution, potentially affecting treatment outcomes in both in vitro and in vivo settings. Further exploration may focus on pathogen-specific interactions, host immune responses, dosing parameters, and safety profiles in preclinical and clinical trial designs.

Index Terms— Phytoconstituents, Urinary tract infections, Anti-biofilm potential, Anti-inflammatory activity, Nano formulation strategies, Plant-derived compounds, Bioavailability, Antimicrobial resistance, Drug delivery systems, Experimental therapeutics

I. INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, affecting people of all ages and genders. They are often caused by pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, which can attach to the urinary tract and form protective biofilms. These biofilms make infections more persistent and resistant to conventional antibiotics, complicating treatment and increasing the risk of recurrence.

Inflammation is another key factor in UTI progression. Chronic inflammatory responses can damage urinary tract tissues and worsen symptoms, while antibiotics alone may not sufficiently control both bacterial growth and inflammation. This has highlighted the need for alternative or complementary treatment approaches.

Phytoconstituents—naturally occurring compounds from plants—have shown potential in addressing these challenges. Bioactive compounds like flavonoids, tannins, terpenoids, phenolic acids, and alkaloids may prevent bacterial adhesion, disrupt biofilm formation, and reduce inflammatory responses. Their multi-targeted actions make them promising candidates for managing UTIs.

1. Anatomy of Urinary System

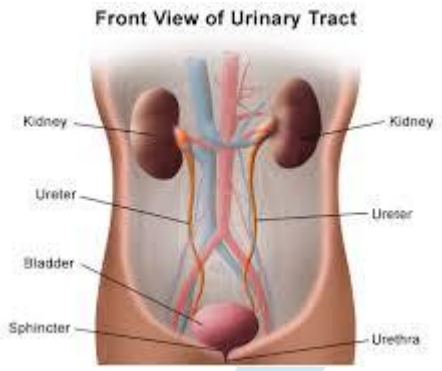


Fig : 1 Front view of Urinary tract [0]

1.1 Filtration Process [0]

The urinary system helps the body remove waste by filtering blood and producing urine. Its main organs are the kidneys, renal pelvis, ureters, bladder, and urethra. The kidneys eliminate liquid waste such as urea, maintain water and electrolyte balance, regulate blood pressure, support red blood cell production through erythropoietin, and preserve acid-base equilibrium. Urea, formed from the breakdown of proteins in food, is transported in the blood to the kidneys and excreted in urine.

1.2 Kidney and urinary system parts and their functions [0]

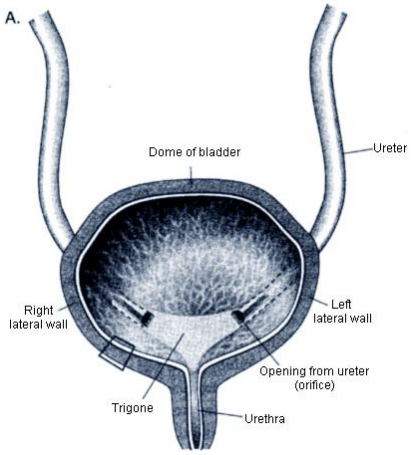


Fig 2: Anatomy of the Human Urinary Bladder and Ureter Openings [0]

Part	Description
Kidneys	Bean-shaped organs that filter blood, remove waste, balance fluids, and produce hormones like erythropoietin.
Nephrons	Functional units of the kidney that filter blood, reabsorb nutrients, and form urine.
Glomerulus	Network of tiny blood capillaries in nephrons where blood filtration begins.
Renal Tubule	Tube in nephrons where water, salts, and nutrients are reabsorbed into the blood.
Renal Pelvis	Funnel-shaped structure that collects urine from the kidney before sending it to ureters.
Ureters	Narrow muscular tubes that transport urine from kidneys to the bladder using peristalsis.
Bladder	Hollow, muscular organ that stores urine until ready to be expelled.
Trigone	Triangular region in the bladder that directs urine toward the urethra.
Sphincter Muscles	Circular muscles controlling the release of urine from the bladder.
Urethra	Tube that carries urine from the bladder out of the body during urination.

Table 1: Kidney and urinary system parts and their functions [1]

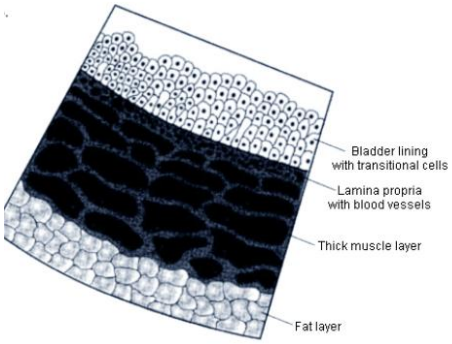


Fig. 3: Histological diagram of the urinary bladder wall. [0]

This diagram illustrates a histological view of the urinary bladder wall. The layers, moving from the inner lumen outward, include: [0]

1. **Transitional epithelium (urothelium)** – A specialized lining that can stretch as the bladder fills.
2. **Lamina propria** – A connective tissue layer containing blood vessels and nerves, providing support to the epithelium.
3. **Detrusor muscle** – A thick layer of smooth muscle responsible for bladder contraction during urination.
4. **Adipose tissue** – A fat layer surrounding the bladder, offering cushioning and structural support.

This cross-section depicts the overall structure and organization of the bladder wall.

2. **Epidemiology & clinical burden of UTIs**

2.1Symptomatic UTI

UTIs are very common among sexually active women and are much more frequent in women than men. About 1 in 3 women will have at least one UTI diagnosed by a clinician requiring antimicrobial treatment by age 24, and 40–50% of women will experience at least one UTI during their lifetime **[2,3,4,5,6]**

2.2Pediatrics

UTIs occur less frequently in prepubertal children: approximately 3% of girls and 1% of boys are affected **[7].**

2.3 Incidence by age group:[9]

Infancy: Girls 0.4–1.0%	Boys 0.188% (circumcised) / 0.702% (uncircumcised)
Age 1–5 years: Girls 0.9–1.4%	Boys 0.1–0.2%
Cumulative incidence by age 6: Girls 6.6%	Boys 1.8%
School age: Girls 0.7–2.3%	Boys 0.04–0.2%

Table 2: Incidence of urinary tract infection among children [9]

2.4 Uncomplicated UTI

Acute uncomplicated UTI (cystitis) in nonpregnant, nonobstructed adult women is usually benign with minimal long-term effects. However, short-term impacts include 6.1 symptomatic days, 2.4 days of restricted activity, and 0.4 days of bed rest **[8].**

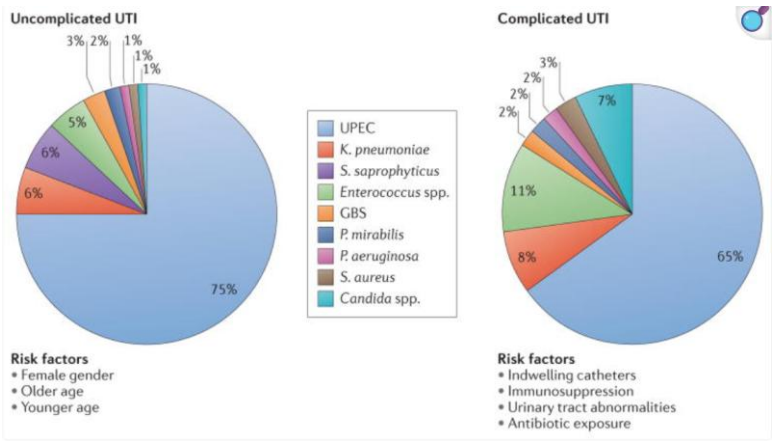


Fig 4: Epidemiology of urinary tract infections [83]

2. **Uropathogenic Escherichia coli (UPEC): Primary Cause of Urinary Tract Infections**

Uropathogenic E. coli (UPEC) is the main pathogen responsible for urinary tract infections (UTIs), causing about 80% of uncomplicated cases, 95% of community-acquired infections, and roughly half of hospital-acquired infections, making it the leading agent in both complicated and uncomplicated UTIs [**10].**

UPEC are extraintestinal pathogenic strains of E. coli, typically originating from the gut **[10,11].** Studies show that UTI-causing isolates often match rectal isolates from the same individual, indicating the intestine serves as a primary reservoir **[12]**. The urinary tract presents a challenging environment for bacterial survival due to urine flow and innate immune defenses. Nevertheless, UPEC use multiple virulence strategies—such as fimbrial and nonfimbrial adhesins, curli, lipopolysaccharides, capsules, flagella, toxins, two-component regulatory systems, and iron acquisition systems—to colonize and persist (8). These virulence factors can be spread through plasmids, transposons, bacteriophages, and pathogenicity islands **[14].** Transcriptomic analyses confirm that many virulence genes are actively expressed during infection, although significant diversity exists among UPEC strains **[14,13].**

3.1 The pathogenesis of UPEC involves several stages [11,14,13]:

1. **Initial colonization:** E. coli from the gut colonizes the periurethral and vaginal areas and the urethra.
2. **Bladder invasion:** Some bacteria become motile and ascend into the bladder, growing as free-floating (planktonic) cells. Adhesins allow them to attach to bladder facet cells.
3. **Intracellular bacterial communities (IBCs):** UPEC invade facet cells and replicate rapidly, forming IBCs that may contain up to 10^5 bacteria per cell.
4. **Host immune response:** The presence of UPEC triggers inflammation, including neutrophil recruitment, cytokine production, exfoliation of infected cells, and production of reactive oxygen and nitrogen species.
5. **Quiescent reservoirs:** Some bacteria invade immature bladder cells, forming dormant reservoirs that are resistant to many antibiotics and may later reactivate, causing recurrent UTIs.
6. **Spread and complications:** UPEC can revert to motile forms, infect new bladder cells, ascend to the kidneys causing pyelonephritis, or enter the bloodstream causing bacteremia/septicemia.

UPEC's ability to survive host defenses, form IBCs, and establish quiescent reservoirs contributes to both recurrent and severe urinary tract infections **[11,14,13]**

3.2 Characteristic Features of ESKAPE Pathogens

Category	Details	Refrence
Enterococcus faecium	Causes healthcare-associated infections; increasingly resistant to vancomycin (VREfm); outbreaks often prolonged (~11 months); treated with second-line drugs like daptomycin or tigecycline	**[15,16,17]**
Methicillin-Resistant Staphylococcus aureus (MRSA)	HA-MRSA: bloodstream infections, pneumonia; CA-MRSA: skin and soft tissue infections; BORSA strains show borderline oxacillin resistance	**[18,19,20]**
Klebsiella pneumoniae	Carbapenem-resistant (CRKP) and hypervirulent (hvKP) strains; high mortality; hypermucoviscous phenotype in hvKP	**[21,22,23,24]**
Acinetobacter baumannii	Hospital-acquired pathogen; MDR and PDR strains; resistant to β-lactams, carbapenems, and polymyxins	**[25,26]**
Pseudomonas aeruginosa	Opportunistic pathogen; nosocomial and community-acquired infections; broad adaptability, antibiotic evasion	**[27]**
Enterobacter species	ICU and neonatal infections; MDR and PDR strains; colistin resistance and undetectable subpopulations	**[28,29]**

3.3 Phytochemicals with Antibacterial & Antibiofilm Activity

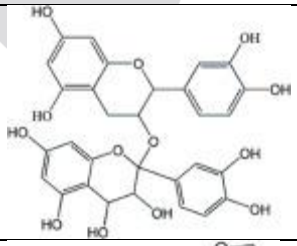
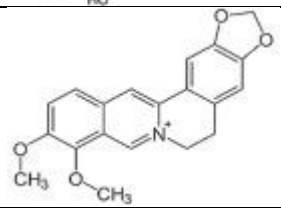
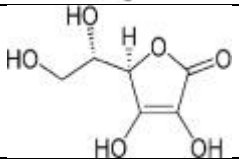
Alkaloids	Examples: Reserpine; inhibit efflux pumps (EP) and biofilm genes (icaA, AgrA, Bap); effective against *S. aureus*, *K. pneumoniae*	[30,31,32]
Flavonoids	Examples: Hesperidin, Quercetin, Fisetin; damage cytoplasmic membrane, inhibit quorum sensing, downregulate energy metabolism; target *A. baumannii*, *Vibrio* sp.	[33,34,35]
Saponins	Examples: Tea saponins, Quillaja saponin; downregulate biofilm-associated genes (srtA, ALS3); can synthesize AgNPs for antibiofilm activity	[36,37,38]
Tannins	Examples: Tannic acid, Penthorum chinense tannins; inhibit quorum sensing, reduce EPS/eDNA secretion; target *P. aeruginosa*, *S. aureus*	[39,40]
Phenolics	Examples: Protocatechuic acid, p-hydroxybenzoic acid; disrupt biofilm matrix, motility, and quorum sensing; target *P. aeruginosa*	[41,42,43,44]
Phytochemicals against *M. tuberculosis*	Terpenoids, flavonoids, alkaloids, tannins, phenols; inhibit nucleic acid synthesis, fatty acid production; active against drug-resistant strains	[45,46,47,48,49,50]

Table : 3 Details of ESKAPE Pathogens

3.5 Herbs management in Urinary Tract Infection

Several herbs have been traditionally used to support urinary tract health and may offer benefits in preventing or managing urinary tract infections (UTIs). While these remedies can be helpful, they should not replace medical treatment, especially for active infections. Always consult a healthcare professional before using herbal supplements.

3.5.1 List of phytochemicals, structure, and pharmacological activity of herbal drugs for the treatment of urinary tract infections (UTIs).

Herbal Drug	Phytochemical	Structure	Pharmacological effects	Refs.
Vaccinium macrocarpon	Proanthocyanidins		Prevents sticking of bacteria to uroepithelial cells, reducing the risk of UTIs.	**[51]**
Hydrastis canadensis	Berberine		Berberine has anti-microbial properties, inhibiting the development of bacteria responsible for UTIs.	**[52]**
Emblica officinalis	Ascorbic acid (vitamin C)		Antimicrobial and antioxidant properties help prevent and manage UTIs.	**[53]53**

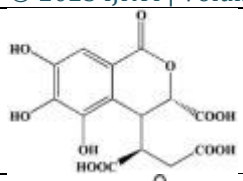
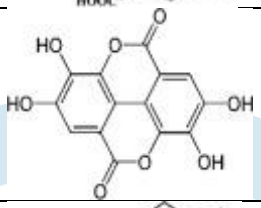
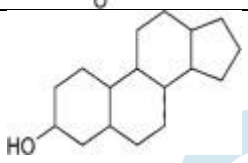
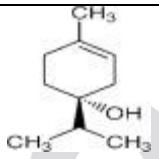
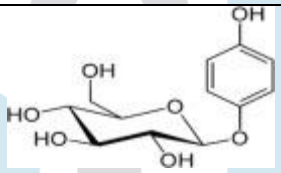
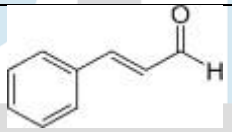
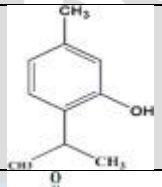
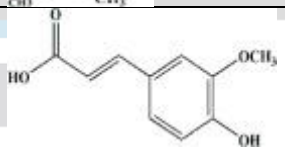
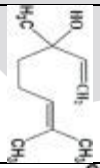
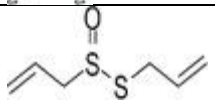
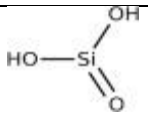
Terminalia chebula	Chebulic acid		Digestive tonic, laxative, antioxidant, antimicrobial, and anti-inflammatory.	**[54]**
Terminalia bellirica	Ellagic acid		Digestive tonic, laxative, antioxidant, antimicrobial, and anti-inflammatory.	**[55]**
Ficus racemose	Sterols		Antimicrobial, anti-inflammatory, and diuretic properties, which can help treat UTIs.	**[56]**
Melaleuca alternifolia	Terpinen-4-ol		It has proven antibacterial properties against uropathogen bacteria (*E. coli*).	**[57]**
Arctostaphylos uva-ursi	Arbutin		Arbutin has antimicrobial activity, and it can inhibit the development of bacteria responsible for UTIs.	**[58]**
Cinnamomum verum	Cinnamaldehyde		It has shown inhibitory effects against various bacteria, including uropathogens (*E. coli*).	**[59]**
Origanum vulgare	Carvacrol		It has proved antimicrobial effect against a wide range of bacteria, as uropathogens.	**[60]**
Taraxacum officinale	Ferulic acid		The diuretic effect helps increase urine production, flushing out bacteria from the urinary tract.	**[61]**
Coriandrum sativum	Linalool		Antimicrobial properties help inhibit the growth of bacteria responsible for UTIs.	**[62]**
Allium sativum	Allicin		Antimicrobial, antifungal, anti-inflammatory, cardiovascular health, and immune support.	**[63]**
Equisetum Arvense	Silicic acid		Horsetail acts as a diuretic,increasing urine flow and helping to flush out bacteria.	**[64]**

Table 4: List of phytochemicals

3.6 Phytoconstituent classes & representative molecules

A range of plant-based bioactive molecules have shown notable potential in tackling biofilms and inflammation caused by uropathogens such as *E. coli* and clinically important ESKAPE organisms. These compounds work through several complementary strategies, including blocking bacterial attachment to host tissues, interfering with quorum sensing signals, limiting the production of extracellular polymeric substances (EPS), and regulating inflammatory pathways within the host. Evidence for these effects comes largely from in-vitro studies and animal models, with some clinical investigations also supporting their use. Despite their promise, real-world application is often influenced by factors like poor bioavailability, differences in formulation, and variability

in study design. The sections that follow summarize the major classes of these phytochemicals, detailing their mechanisms, supporting data, and key limitations.

1) Proanthocyanidins (PACs) — Cranberry (A-type PACs)

Mechanism (anti-biofilm / anti-adhesion):

A-type PACs prevent P-fimbriated *E. coli* from attaching to uroepithelial cells, which limits initial colonization and subsequent biofilm development**. [65,66]**

Key evidence:

In-vitro work consistently demonstrates anti-adhesion effects, while randomized clinical trials and meta-analyses report reductions in recurrent UTIs. The degree of benefit varies based on PAC concentration, formulation, and target population. Reviews acknowledge that benefits apply mainly to prevention rather than treatment of active infections**.[67,68]**

2) Flavonoids / Polyphenols — Quercetin, Catechins (EGCG), Rutin

Mechanisms:
These compounds interfere with quorum sensing, decrease EPS production, and reduce motility. They also downregulate inflammatory mediators through NF-κB and MAPK pathways, leading to decreased levels of TNF-α and IL-1β.**[69,70]**
Key evidence:
Laboratory studies show strong effects on biofilm suppression, signaling interference, and inflammatory marker reduction. Animal data support anti-inflammatory action, while human studies are fewer and vary in outcomes.**[70,71]**

3) Alkaloids — Berberine

Mechanisms:
Berberine disrupts microbial membrane stability and electrical potential, suppresses EPS production, interferes with quorum sensing, and targets cell division proteins. It also dampens inflammatory signaling pathways. **[72]**
Key evidence:
Extensive in-vitro research demonstrates broad-spectrum antibiofilm effects. In vivo studies and nanoparticle-based formulations show enhanced delivery and activity, though conventional uptake remains limited.**[72,73]**

4) Curcuminoids — Curcumin

Mechanisms:
Curcumin interferes with biofilm structure and quorum-sensing circuits while exerting strong anti-inflammatory activity through downregulation of NF-κB, COX-2, and oxidative stress pathways.**[74]**
Key evidence:
Repeated in-vitro findings confirm effects on both biofilm disruption and inflammation control. Animal experiments show significant reductions in biofilm load and tissue inflammation. However, low bioavailability necessitates delivery innovations (e.g., nanoformulations, carriers).**[75]**

5) Terpenoids / Essential Oils — Carvacrol, Thymol, Eugenol

Mechanisms:
These molecules compromise microbial membranes, inhibit EPS production, and disrupt quorum sensing. They can also enhance the action of antibiotics through synergistic effects**.[76,77]**
Key evidence:
Studies consistently show in vitro inhibition of biofilm development and evidence of synergy with antimicrobial agents. Animal models confirm a reduction in biofilm burden. However, volatility, irritation potential, and variability in composition remain challenges. **[77]**

6) Phenolic Glycosides — Arbutin (Uva-ursi / Bearberry)

Mechanisms:
Once metabolized, arbutin yields hydroquinone derivatives in urine, which exert antiseptic effects and may inhibit bacterial survival and biofilm formation in the urinary tract.**[78,79]**
Key evidence:
Laboratory studies show antibacterial and antibiofilm effects, while historical use and small clinical trials indicate symptom relief

and supportive roles in urinary tract care. Findings are mixed, and modern data are limited.**[79,80]**

7) Xanthones / C-glucosides — Mangiferin

Mechanisms:
Mangiferin reduces EPS formation, interferes with adhesion-related enzymes, and limits biofilm matrix development. It also displays antioxidant and anti-inflammatory properties. **[81,82]**
Key evidence:
Multiple in-vitro studies document reductions in biofilm formation and EPS output. Early-stage formulation studies (e.g., smart delivery systems) show potential, though clinical data are largely lacking.**[81,82]**

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