



ISSN Print: 2664-9926
 ISSN Online: 2664-9934
 NAAS Rating: 4.82
 IJBS 2025; 7(7): 102-108
www.biologyjournal.net
 Received: 02-06-2025
 Accepted: 05-07-2025

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Biochemical and molecular mechanisms underlying the role of dietary polyphenols in modulating uropathogenic virulence in women with UTIs

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DOI: <https://www.doi.org/10.33545/26649926.2025.v7.i7b.418>

Abstract

Urinary tract infections (UTIs) are a common and recurrent health issue, especially in women, often requiring repeated antibiotic use that contributes to antimicrobial resistance. Uropathogenic *Escherichia coli* (UPEC), the leading cause of UTIs, can adhere to and invade bladder epithelial cells, forming intracellular bacterial communities that evade immune detection and antibiotic treatment. With rising resistance concerns, attention has turned to non-antibiotic alternatives such as dietary polyphenols. Found in fruits, vegetables, tea, and wine, polyphenols are plant-derived compounds with antioxidant, anti-inflammatory, and antimicrobial effects. Cranberry proanthocyanidins, in particular, prevent UPEC adhesion to urinary tract cells, reducing infection risk. Polyphenols exert multiple actions: inhibiting biofilm formation, disrupting quorum sensing, modulating bacterial enzyme activity, and enhancing epithelial barrier integrity. Additionally, they influence host immune responses by downregulating inflammatory cytokines and activating protective signalling pathways. While clinical and *in vitro* studies support their potential in reducing UTI frequency and severity, challenges remain, including low bioavailability and individual variability in response. Further research is needed to optimize formulations and delivery systems. Despite current limitations, incorporating polyphenol-rich foods into preventive healthcare represents a promising, sustainable strategy to manage UTIs and reduce dependence on antibiotics.

Keywords: Urinary tract infections, dietary polyphenols, uropathogenic *E. coli*, molecular mechanisms, biofilm, virulence

1. Introduction

Urinary tract infections (UTIs) are a prevalent health issue, particularly among women, with significant recurrence rates and clinical implications. Traditional antibiotic therapies, while effective, are increasingly limited by rising antimicrobial resistance, necessitating alternative strategies. Dietary polyphenols, such as those found in cranberries, offer promising potential in modulating uropathogenic virulence through various biochemical and molecular mechanisms. Given the growing urgency for non-antibiotic approaches to manage recurrent UTIs and combat resistance, this paper aims to review the mechanistic roles of dietary polyphenols in preventing and controlling UTIs, while identifying their therapeutic relevance and research gaps (Lee, 2023) ^[1].

1.1 Prevalence and Recurrence of UTIs in Women

UTIs are among the most common bacterial infections, affecting over 40 percent of women at least once in their lifetime, with 30% experiencing recurrent infections within six months (Lee, 2023) ^[1]. The recurrence of UTIs poses a significant health burden, often leading to long-term antibiotic use, which can contribute to antibiotic resistance (Scribano *et al.*, 2021) ^[2].

1.2 Clinical Significance and Limitations of Antibiotic Therapy

Antibiotics are the standard treatment for UTIs, but their overuse has led to the emergence of multidrug-resistant uropathogens (Kucheria *et al.*, 2023) ^[3]. Long-term antibiotic prophylaxis, while effective, can result in resistance not only to the prescribed antibiotic but also to other antimicrobial agents (Forbes *et al.*, 2018) ^[4].

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1.3 Rising Antimicrobial Resistance and the Need for Alternative Strategies

The World Health Organization has identified antibiotic resistance as a major public health challenge, prompting the exploration of non-antibiotic alternatives (Kucheria *et al.*, 2023) [3]. Non-antibiotic strategies, such as antiadhesive treatments, immunomodulation therapies, and probiotics, are being investigated for their potential to manage recurrent UTIs without contributing to resistance (Lee, 2023) [1].

1.4 Overview of Dietary Polyphenols: Definition, Sources, Health Relevance

Polyphenols are natural compounds found in various foods, including cranberries, which are rich in flavonoids and phenolic acids (Llano *et al.*, 2020) [5]. These compounds have demonstrated broad anti-infective properties, including disruption of microbial membranes and inhibition of bacterial adhesion (Ιωάννου & Baliou, 2024) [6].

1.5 Biochemical and Molecular Mechanisms of Dietary Polyphenols

Cranberry polyphenols, particularly A-type proanthocyanidins, inhibit the adhesion of uropathogenic *Escherichia coli* (UPEC) to the urothelium, reducing UTI occurrence (Ιωάννου & Baliou, 2024) [6]; (Khoo & Liu, 2018) [7]. Polyphenols can modulate the integrity and

functionality of the intestinal and urinary barriers, enhancing host defenses against infections (Llano *et al.*, 2024) [8]. Rutin, a specific polyphenol, has shown potential in reducing biofilm formation and bacterial virulence, suggesting its role in developing novel antimicrobials (Ivanov *et al.*, 2022) [9]. While dietary polyphenols present a promising alternative to antibiotics in managing UTIs, challenges remain in optimizing their use. Issues such as bioavailability, optimal dosages, and potential side effects need further investigation. Additionally, the complexity of UTI pathophysiology and the adaptive evolution of uropathogens necessitate a multifaceted approach, combining dietary interventions with other non-antibiotic strategies. Continued research is essential to fully understand and harness the potential of polyphenols in UTI prevention and treatment.

2. Uropathogenic Mechanisms and Emerging Dual-Target Strategies in UTIs

Table 1 summarizes the key uropathogenic mechanisms involved in UTIs, including bacterial strategies like adhesion, biofilm formation, and immune evasion, alongside emerging host-and pathogen-targeted therapeutic approaches such as the dual-target strategy. This integrated understanding supports the development of more effective interventions for recurrent and chronic UTIs.

Table 1: Uropathogenic Mechanisms and Therapeutic Insights in UTIs

Mechanism/Target	Description	Key References
Major Uropathogens and Virulence Factors	Uropathogenic <i>E. coli</i> (UPEC) is the leading cause of UTIs, possessing virulence traits like type 1 fimbriae, toxins, and siderophores for colonization and survival.	(Lewis <i>et al.</i> , 2024) [10]; (Maisto <i>et al.</i> , 2023) [11]
Biofilm Formation and Chronic Infection	Biofilms protect bacteria from antibiotics and immune defenses. Catheter-associated biofilms increase recurrence and antimicrobial resistance.	(Lewis <i>et al.</i> , 2024) [10]
Intracellular Reservoirs and Host Evasion	UPEC forms intracellular bacterial communities (IBCs) and manipulates host autophagy, enabling survival and recurrence despite treatment.	(Lewis <i>et al.</i> , 2024) [10]
Dual-Target Strategy	A strategy targeting both bacterial virulence (adhesion, quorum sensing) and host immunity (inflammation, oxidative stress) to reduce UTI severity and recurrence.	(Ivanov <i>et al.</i> , 2022) [9]; (Maisto <i>et al.</i> , 2023) [11]
Pathogen-Specific Targets	Focuses on disrupting bacterial adhesion and quorum sensing gene expression (lasI, lasR, rhII, rhIR). Targets include <i>P. aeruginosa</i> and <i>E. faecalis</i> .	(Ivanov <i>et al.</i> , 2022) [9]
Host-Targeted Approaches	Polyphenols reduce TNF-α and IL-6, boost innate immunity via TLR activation, and enhance mucosal defenses.	(Ιωάννου & Baliou, 2024) [6]
Expected Outcomes and Limitations	Aims to reduce recurrence and improve outcomes in high-risk patients. Challenges include resistance to quorum sensing inhibitors and individualized immune responses.	(Ivanov <i>et al.</i> , 2022) [9]

Abbreviations: UPEC-Uropathogenic Escherichia coli; UTI-Urinary Tract Infection; IBC-Intracellular Bacterial Community; TNF-α-Tumor Necrosis Factor-alpha; IL-6-Interleukin-6; TLR-Toll-Like Receptor; P. aeruginosa-Pseudomonas aeruginosa; E. faecalis-Enterococcus faecalis

3. Dietary Polyphenols: Structural Classes, Dietary Sources, and Systemic Health Implications

Table 2 summarizes the key categories of dietary polyphenols, their major subtypes and dietary sources, and outlines their core biochemical and therapeutic functions. It highlights the structural diversity of polyphenols such as flavonoids, phenolic acids, stilbenes, and lignans and connects these chemical classes to specific health benefits. The table also addresses polyphenol bioavailability, their metabolism via gut microbiota, and systemic impacts, particularly in the context of urinary tract infection (UTI) prevention and immune modulation.

4. Biochemical Actions of Polyphenols Against Uropathogens

Polyphenols exhibit multifaceted antimicrobial actions

against uropathogens, positioning them as promising alternatives to conventional antibiotics. These actions include inhibition of bacterial adhesion, disruption of membrane integrity, quorum sensing interference, suppression of biofilm formation, and modulation of virulence-associated enzymes, as illustrated in Fig. 1 (Li *et al.*, 2022) [20].

4.1 Anti-Adhesion Mechanisms

Cranberry-derived compounds like myricetin and quercetin inhibit the adherence of uropathogenic *E. coli* (UPEC) to uroepithelial cells. Myricetin shows potent activity with IC₅₀ values of 13.2 μM (P-type) and 5.50 μM (type-1 fimbriae). Proanthocyanidins (PACs) from cranberries exhibit strong anti-adhesion effects (Li *et al.*, 2022) [20].

Table 2: Classification and Functional Overview of Dietary Polyphenols

Category	Subtypes/Sources	Key Functional Roles	References
Definition & Structure	Compounds with multiple phenol units and hydroxyl groups	Antioxidant capacity due to chemical structure (aromatic rings with hydroxyls)	(Rudrapal <i>et al.</i> , 2024) ^[12] ; (Ciupei <i>et al.</i> , 2024) ^[13]
Flavonoids	Flavonols, flavanols, flavones, flavanones, isoflavones, anthocyanins	Broad-spectrum bioactivity: antimicrobial, anti-inflammatory, antioxidant	(Lorenzo <i>et al.</i> , 2021) ^[14] ; (Durazzo <i>et al.</i> , 2019) ^[15]
Phenolic Acids	Hydroxycinnamic acids (e.g., caffeic acid)	Prevent oxidative stress and microbial growth	(Lorenzo <i>et al.</i> , 2021) ^[14]
Stilbenes	Resveratrol (from grapes)	Anti-inflammatory, antioxidant, and cardiovascular protection	(Durazzo <i>et al.</i> , 2019) ^[15]
Lignans	Found in flaxseed, grains, and vegetables	Hormonal balance, antioxidant effects	(Durazzo <i>et al.</i> , 2019) ^[15]
Cranberries	Rich in flavonoids and phenolic acids	Anti-adhesive against UPEC; prevents UTI onset	(Rudrapal <i>et al.</i> , 2024) ^[12]
Pomegranate	High in ellagic acid	Antimicrobial and anti-inflammatory	(Truzzi <i>et al.</i> , 2021) ^[16]
Green Tea	High catechin content (e.g., EGCG)	Antioxidant, membrane disruption of pathogens	(Rana <i>et al.</i> , 2022) ^[17]
Grapes	Contains resveratrol	Cardiovascular benefits, antimicrobial action	(Rana <i>et al.</i> , 2022) ^[17]
Bioavailability	Low oral absorption; metabolized in liver & gut	Microbiota transform into active metabolites crucial for systemic and urinary tract effects	(Lorenzo <i>et al.</i> , 2021) ^[14] ; (Truzzi <i>et al.</i> , 2021) ^[16]
Systemic Impact	Gut-health modulation, redox balance, immune regulation	Relevant for UTI prevention and general anti-inflammatory mechanisms	(Sejbuk <i>et al.</i> , 2024) ^[18] ; Lippolis <i>et al.</i> , 2023 ^[19]

Abbreviations: UPEC-Uropathogenic Escherichia coli; UTI-Urinary Tract Infection.

4.2 Membrane Disruption

Tea polyphenols disrupt bacterial membranes, causing leakage and oxidative stress due to ROS accumulation (Zhong *et al.*, 2023) ^[21]. Rutin also compromises membrane permeability (Ivanov *et al.*, 2022) ^[9].

4.3 Quorum Sensing Inhibition

Polyphenols like rutin interfere with bacterial communication systems (quorum sensing), downregulating genes like *lasI*, *lasR*, *rhlI*, and *rhlR* in *Pseudomonas aeruginosa*, reducing virulence without resistance pressure (Higuera-Ciapara *et al.*, 2024) ^[22]; (Ivanov *et al.*, 2022) ^[9].

4.4 Biofilm Suppression

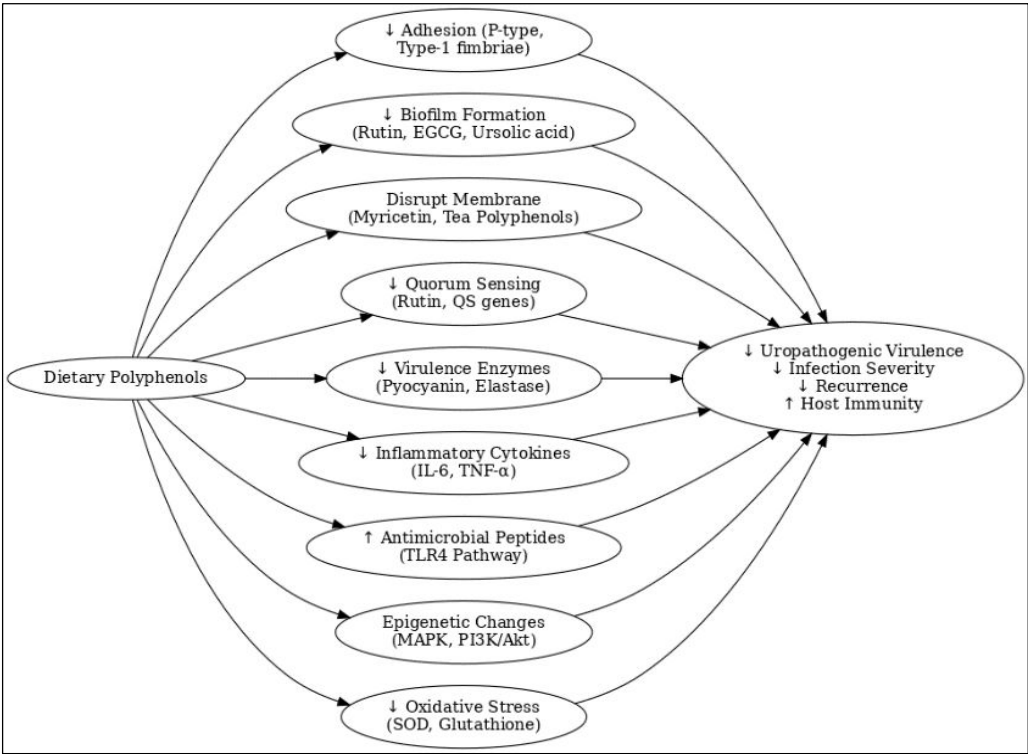
Compounds such as rutin, EGCG, and ursolic acid reduce

biofilm biomass and matrix synthesis, limiting bacterial persistence in chronic infections (Ivanov *et al.*, 2022) ^[9]; Sycz *et al.*, 2022) ^[23]; (Hengge, 2019) ^[24].

4.5 Enzyme Modulation

Rutin downregulates bacterial enzymes like protease, pyocyanin, and elastase, impeding biofilm formation and virulence (Ivanov *et al.*, 2022) ^[9]; (Buchmann *et al.*, 2023) ^[25].

While promising, the antimicrobial effects of polyphenols vary across bacterial strains and compound types, necessitating further studies on structure-function relationships and synergistic combinations with existing therapies.



Source: Adapted by the author based on data from Li *et al.* (2022); Ivanov *et al.* (2022); Zhong *et al.* (2023); Higuera-Ciapara *et al.* (2024); Buchmann *et al.* (2023); Sycz *et al.* (2022); Hengge (2019); Lippolis *et al.* (2023) ^[21, 9, 21, 22, 23, 24, 25, 19]

Fig 1: Mechanistic Overview of Dietary Polyphenols in Reducing Uropathogenic Virulence

5. Molecular Modulation of Host Response by Polyphenols

Polyphenols modulate the host immune system through multiple molecular pathways, enhancing the body's defenses against infections and inflammation. Their mechanisms include downregulating inflammatory cytokines, boosting antimicrobial peptides, modulating gene expression, and acting as potent antioxidants (Shakoor *et al.*, 2021) ^[26]; (Yahfoufi *et al.*, 2018) ^[27].

5.1 Cytokine Suppression

Polyphenols like curcumin and quercetin inhibit inflammatory mediators such as IL-6 and TNF- α by targeting NF- κ B and JAK/STAT pathways. This has shown therapeutic benefits in inflammatory diseases like IBD (Vaghari-Tabari *et al.*, 2022) ^[28]; (Ismail *et al.*, 2024) ^[29].

5.2 Immune Activation

These compounds enhance innate immunity by modulating Toll-like receptors (especially TLR4) and supporting the function of dendritic cells, macrophages, and T cells (Yu *et al.*, 2022) ^[30]; (Shakoor *et al.*, 2021) ^[26].

5.3 Gene and Epigenetic Modulation

Polyphenols influence signalling pathways such as MAPK and PI3K/Akt, inducing beneficial gene expression and epigenetic modifications in uroepithelial cells (Yahfoufi *et al.*, 2018) ^[27].

5.4 Antioxidant Defense

By inhibiting enzymes like xanthine oxidase and upregulating antioxidant enzymes such as SOD and glutathione peroxidase, polyphenols mitigate oxidative stress and protect tissues from damage (Yahfoufi *et al.*, 2018) ^[27]; (Vaghari-Tabari *et al.*, 2022) ^[28].

While promising, these effects can vary due to differences in polyphenol type, dosage, and individual metabolism. More

clinical studies are needed to clarify their long-term safety and efficacy in infectious and inflammatory disease contexts (Ismail *et al.*, 2024) ^[29]; (Yu *et al.*, 2022) ^[30].

6. Polyphenolic Compounds and Their Role in UTI Therapy

Table 3 presents various dietary polyphenols such as proanthocyanidins (PACs), epigallocatechin gallate (EGCG), resveratrol, and quercetin that have been investigated for their potential role in preventing and managing urinary tract infections (UTIs). These compounds exhibit multiple antimicrobial mechanisms, including inhibition of bacterial adhesion, suppression of biofilm formation, disruption of microbial membranes, and modulation of immune responses (Williams *et al.*, 2023) ^[31]; (Li *et al.*, 2022) ^[20].

- **Proanthocyanidins (PACs)**, primarily derived from cranberries, are the most extensively studied polyphenols in UTI contexts. They prevent adhesion of p-fimbriated *E. coli* to uroepithelial cells, a key step in UTI pathogenesis. *in vitro* studies have confirmed their anti-adhesive effects, and clinical trials have shown reduced UTI incidence in women and children. A meta-analysis indicates that daily intake of 36 mg of PACs can reduce UTI risk by approximately 18 percent (Xiong *et al.*, 2024) ^[32].
- **Epigallocatechin Gallate (EGCG)**, found in green tea, exerts antimicrobial effects by disrupting bacterial membranes and acting as an antioxidant. While specific UTI studies are limited, its general efficacy against bacterial pathogens is well documented (Ivanov *et al.*, 2022) ^[9].
- **Quercetin** and **resveratrol**, found in various fruits and vegetables, have demonstrated immunomodulatory, anti-inflammatory, and anti-adhesion effects. Quercetin, in particular, has shown promising results *in vitro* against UPEC adhesion and biofilm formation.

Table 3: Summary of Key Polyphenols, Their Mechanisms and Supporting Evidence is Provided

Polyphenol	Source	Mechanism of Action	Evidence Type	References
Proanthocyanidins	Cranberries	Anti-adhesive, anti-biofilm	<i>In vitro</i> , clinical studies	(Li <i>et al.</i> , 2022; Williams <i>et al.</i> , 2023; Llano <i>et al.</i> , 2019; Xiong <i>et al.</i> , 2024) ^[20] , ^[31] , ^[33] , ^[32]
Epigallocatechin Gallate (EGCG)	Green Tea	Membrane disruption, antioxidant	General antimicrobial research	(Ivanov <i>et al.</i> , 2022; Zhong <i>et al.</i> , 2023) ^[9] , ^[21]
Resveratrol	Grapes, Berries	Immunomodulatory, anti-inflammatory	General antimicrobial research	(Durazzo <i>et al.</i> , 2019; Yahfoufi <i>et al.</i> , 2018) ^[15] , ^[27]
Quercetin	Onions, Apples	Anti-adhesive, antimicrobial	<i>In vitro</i> studies	(Li <i>et al.</i> , 2022; Ivanov <i>et al.</i> , 2022) ^[20] , ^[9]

7. Research Gaps and Limitations

Despite encouraging findings, the application of dietary polyphenols in UTI prevention and treatment is limited by several critical research gaps. Key issues include inconsistent bioavailability, lack of standardized clinical trials, suboptimal delivery systems, and incomplete understanding of host-microbiome interactions.

7.1 Bioavailability and Interindividual Response

Polyphenol metabolism and efficacy vary greatly between individuals due to differences in gut microbiota, genetics, and physiological factors (Favari *et al.*, 2024) ^[34]; (Morand, 2024) ^[35]. Microbial diversity influences the conversion of polyphenols into bioactive metabolites, leading to inconsistent outcomes (Ho *et al.*, 2019) ^[36].

7.2 Limited Clinical Trials and Lack of Standardization

Existing clinical data on polyphenols in UTI management are sparse and often suffer from methodological flaws, including small cohorts and lack of control (Maisto *et al.*, 2023) ^[11]. Variability in dosing, formulation, and outcome measures further undermines reproducibility (Karp, 2018) ^[37].

7.3 Targeted Delivery and Synergistic Potential

Most polyphenols are poorly absorbed and rapidly metabolized, limiting their action at the urinary tract. Targeted delivery systems remain underdeveloped (Peron *et al.*, 2020) ^[38]. Combining polyphenols with complementary agents like probiotics may enhance their efficacy, but this synergy is not yet fully explored (Ioánnou & Baliou, 2024) ^[6].

7.4 Host Genetics and Microbiome Dynamics

Genetic polymorphisms and microbial ecology play a crucial role in polyphenol metabolism and efficacy, yet they remain largely unexplored in current UTI-related studies (Morand, 2024 ^[35]; (Piwowarski *et al.*, 2021) ^[39]).

Key Points

Addressing these gaps will require:

- Multi-omic analyses (genomics, metabolomics, microbiomics)
- Personalized clinical trials
- Standardized and bioavailable formulations

These efforts are essential to advance polyphenol-based interventions in UTI therapy.

8. Future Perspectives

Advancements in biotechnology and integrative health research are opening new frontiers for using polyphenols in UTI management. Nanotechnology, omics-based profiling, and functional nutrition are key drivers of this evolution.

8.1 Antibiotic-Adjunct Potential

Polyphenols such as rutin have demonstrated efficacy in reducing biofilm formation and virulence factor expression in resistant pathogens like *Pseudomonas aeruginosa* (Ivanov *et al.*, 2022). Their combination with nanoparticles enhances antimicrobial potency through membrane disruption and ROS generation (Farhadi *et al.*, 2023) ^[40].

8.2 Smart Delivery Systems

Novel vehicles like solid lipid nanoparticles and liposomes improve site-specific delivery and bioavailability of polyphenols, enhancing retention in bladder tissues and overcoming challenges like rapid clearance (Sarfraz *et al.*, 2022) ^[41].

8.3 Molecular Insights via Omics Tools

Transcriptomic and proteomic studies provide mechanistic understanding of how polyphenols affect pathogen virulence and host immunity (Ivanov *et al.*, 2022) ^[9]; (Kong *et al.*, 2024) ^[42]. These insights enable identification of molecular targets for personalized interventions.

8.4 Diet-Based Prevention Strategies

Polyphenol-rich diets, especially those incorporating cranberries, show promise in reducing bacterial adhesion and infection rates. Integrating these findings into nutritional guidelines can support UTI prevention (Maisto *et al.*, 2023) ^[11].

Section Insight

Future directions include:

- Optimizing nano formulations for clinical use
- Incorporating multi-omic data for targeted therapies
- Developing nutrition-based protocols for long-term management

Collectively, these strategies can position polyphenols as key tools in the fight against antibiotic-resistant UTIs.

9. Conclusion

Dietary polyphenols are emerging as promising agents in the management of urinary tract infections, offering

antimicrobial, anti-inflammatory, and antioxidant effects. These plant-derived compounds target uropathogens through multiple pathways, including disruption of bacterial adhesion, inhibition of biofilms, and modulation of host immune responses.

9.1 Scientific Rationale

Flavonoids and related polyphenols exhibit broad-spectrum activity by disrupting microbial membranes, interfering with quorum sensing and regulating inflammatory pathways (Ιωάννου & Baliou, 2024) ^[6]; (Ivanov *et al.*, 2022) ^[9].

9.2 Therapeutic Insights

Initial clinical studies indicate a reduction in UTI recurrence, especially in women, although further trials are needed to establish optimal formulations and dosing regimens (Ιωάννου & Baliou, 2024) ^[6].

9.3 Renal and Systemic Health Benefits

Beyond infection control, polyphenols may offer kidney protection through their antioxidative and anti-inflammatory properties (Guerreiro *et al.*, 2022) ^[43].

9.4 Future Research Imperatives

Research should focus on enhancing polyphenol bioavailability, exploring nanoparticle-based delivery systems and tailoring interventions based on genetic and microbial profiles (Baptista *et al.*, 2024) ^[44]; (Maisto *et al.*, 2023) ^[11].

9.5 Broader Implications

With rising antimicrobial resistance, integrating polyphenols into standard UTI management protocols—alongside antibiotics, dietary changes, and microbiome-based strategies, may offer a holistic and sustainable solution.

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