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Adhesion-Directed Nutraceutical Intervention for Urinary Tract Health: Clinical Evidence and Mechanistic Rationale for a Cranberry (Vaccinium Macrocarpon) and D-Mannose Combination Formulation

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Abstract: The most common reason for recurrent antibiotic treatments among adult women is recurrent urinary tract infection (rUTI), and thus, the matter of alternative preventives is increasingly urgent. Both cranberry (Vaccinium macrocarpon Aiton) A-type proanthocyanidins (PACs) and D-mannose target different adhesion mechanisms of uropathogenic strains of Escherichia coli (UPEC), either preventing P-fimbrial PapG-globoside interaction or competing with binding mannosylated uroplakin-Ia by type-1 fimbriae via binding their FimH pocket. This narrative review critically appraises the available mechanistic, phytochemical, pharmacokinetic, clinical, microbiomic, pharmacoeconomic, and regulatory evidence pertinent to the combination of these two UTI preventives. The randomised evidence and the Cochrane review allowed concluding that PAC-standardized cranberry preparations reduced the risk of culture-confirmed UTI in women with rUTI by approximately half (relative risk: 0.48-0.77). In contrast, D-mannose monotherapy at the dose of 2 g/day failed to demonstrate efficacy beyond the placebo in the 2024 Hayward trial and the subsequent 2025-2026 pooled analysis. Meanwhile, cranberry (poly) phenols exhibit vascular effects, improving flow-mediated dilation and reducing ambulatory diastolic blood pressure, and combination therapies involving cranberry, D-mannose, and Lactobacillus spp. were associated with consistent efficacy in reducing UTIs and antibiotic consumption. Pharmacoeconomic considerations suggest that non-antibiotic preventives are associated with a higher cost per one six-month course compared to low-dose antibiotic regimens, but they offer significant antimicrobial stewardship benefits. Altogether, the Biotex Life Solutions combination contains D-mannose 500 mg and Vaccinium macrocarpon fruit 10 mg per serving, and thus, it is postulated to reduce UTI risk via blocking both adhesion mechanisms at the submaximal active substance doses, with the additional cranberry-mediated vascular effects. As such, it is reasoned that the combination product, despite its theoretical advantages, will require further clinical substantiation of both cranberry's anti-adhesive mechanism and vascular claims in the context of the specific product formulation.

Keywords: D-mannose; cranberry; *Vaccinium macrocarpon*; proanthocyanidins; FimH; urinary prophylaxis; vascular health.

1. Introduction

Urinary tract infection is one of the most common bacterial conditions in ambulatory practice. The lifetime risk of at least one UTI exceeds 40 % in adult women, and approximately 30 % of index infections recur within six

months [33]. Recurrent disease (rUTI) disproportionately drives outpatient antibiotic prescribing, microbiome perturbation, and selection for resistant uropathogens. The contemporary therapeutic ceiling on long-term antibiotic prophylaxis has therefore motivated a systematic search for non-antibiotic prophylactics.

A unifying mechanistic frame for the leading non-antibiotic candidates is now discernible. Cranberry PACs, D-mannose, *Lactobacillus*-based probiotics, vaginal oestrogens, methenamine hippurate, and FimH antagonists each act on a step along the UPEC colonisation pathway: peri-urethral acquisition; fimbrial adhesion to uroplakins on superficial umbrella cells; intracellular bacterial community formation; persistence in quiescent intracellular reservoirs; and recrudescence from those reservoirs [11–14]. Cranberry A-type PACs primarily block P-fimbrial PapG binding to globoseries glycolipids [17]; D-mannose saturates the FimH mannose-binding pocket to displace type-1 fimbrial binding to mannosylated uroplakin-Ia [7,34,35].

A combination product delivering both actives offers the possibility of broader and more durable anti-adhesion coverage, and the cranberry (poly)phenol component drives secondary vascular-layer benefits — improved endothelial function and modest diastolic blood pressure reductions in pre-hypertensive users — claimed by modern urinary-tract nutraceuticals [23–26]. This review assembles the clinical, mechanistic, pharmacokinetic, microbiomic, pharmacoeconomic, and regulatory evidence for each component individually, for their combination, and for the vascular extension of benefit, and situates the Biotex Life Solutions combination product within the contemporary non-antibiotic prophylaxis landscape.

2. Scope, Sources, and Appraisal Framework

A structured three-stage search of PubMed, PubMed Central, Web of Science, the Cochrane Library, ClinicalTrials.gov, OpenAlex, the FDA and EFSA register of health-claim petitions, and Google Scholar was conducted between 1 January 2016 and 31 July 2026, with no language restriction. Search terms combined "D-mannose," "cranberry," "*Vaccinium macrocarpon*," "proanthocyanidin," "FimH," "uropathogenic *E. coli*," "intracellular bacterial community," "quiescent intracellular reservoir," "recurrent urinary tract infection," "anti-adhesion," "antioxidant," "flow-mediated dilation," "ambulatory blood pressure," "methenamine hippurate," "pharmacoeconomics," and "urobiome."

Evidence was stratified into three tiers. **Tier 1 (highest authority):** RCTs and meta-analyses of cranberry, D-mannose, or combinations for UTI prevention or treatment [4,5,36–39]; the 2022 Cochrane review of D-mannose [1]; the 2023 Cochrane review of cranberry [2]; the 2022 Harding ALTAR non-inferiority RCT [3]; the 2024 Hayward *JAMA Internal Medicine* RCT [4]; the 2025 Stonehouse RCT [5]; and EFSA [40–42] and FDA [43] claim opinions. **Tier 2 (mechanistic):** structural and biochemical studies of FimH and PapG [6–10]; UPEC pathogenesis and QIR biology [11–15]; phytochemistry of *V. macrocarpon* [16–18]; and pharmacokinetic and regulatory-classification work on D-mannose [19,34,35,44,45]. **Tier 3 (vascular extension):** RCTs of cranberry (poly)phenols on endothelial function, arterial stiffness, ambulatory blood pressure, and oxidative stress biomarkers [23–26], with their accompanying meta-analyses [46,47]. Quality was graded using the Cochrane Risk of Bias 2 tool and the GRADE framework.

3. UPEC Pathogenesis as the Molecular Scaffold

3.1 Colonisation, adhesion, invasion, IBC formation, and quiescence

A productive UTI requires UPEC to colonise the peri-urethral area from enteric reservoirs; ascend the urethra; adhere to uroepithelium via fimbrial adhesins; invade superficial umbrella cells; replicate inside the host cytosol as an IBC with biofilm-like organisation; disperse as filamentous bacteria to evade neutrophils; seed QIRs within the uroepithelium; and reactivate to produce recrudescence [12–14]. McLellan and Hunstad summarised this cascade: bacteria that invade bladder epithelium can form quiescent intracellular reservoirs that avoid immune clearance and resist systemic antibiotic treatment, and these persistent UPEC may reactivate to cause the recurrent cystitis so common clinically [12]. Rosen *et al.* [11] identified IBCs in human — not only murine — bladder specimens, substantiating clinical relevance. Garofalo *et al.* [15] documented that the majority of clinical UPEC isolates are competent for IBC formation in the murine model irrespective of specimen source.

This eight-step model has direct product-development implications: anti-adhesion nutraceuticals act at step (iii) by blocking the molecular handshake between fimbrial adhesin and bladder-surface receptor, but they cannot reach bacteria already resident in the QIRs (step vii). A clinically realistic expectation of any cranberry or D-mannose intervention is therefore a reduction in the probability of *new* infection — not clearance of established infection or eradication of established QIR seeding events.

3.2 Dual fimbrial systems as non-redundant pharmacological targets

Type 1 pili, tipped with the FimH adhesin, bind α-D-mannosylated glycans on uroplakin-Ia on superficial bladder cells. P pili, tipped with the PapG adhesin, bind the Galα (1–4) Gal moiety of globoseries glycolipids. UPEC populations in rUTI patients are polyclonal across isolates and across recurrent episodes within the same patient. Hung *et al.* [7] resolved the FimH–mannose crystallographic complex and demonstrated near-complete conservation of the mannose-binding pocket across UPEC populations. Kalas *et al.* [10] described the conformational dynamics between low-affinity "tense" and high-affinity "relaxed" FimH states — the catch-bond phenomenon. Cranberry A-type PACs block the PapG–globoside axis; D-mannose blocks the FimH–mannose axis. The two actives therefore cover complementary layers of a heterogeneous UPEC population, and the combination is mechanistically defensible even when monotherapy against either alone can be circumvented by strain heterogeneity.

4. D-Mannose — Chemistry, Disposition, Pharmacokinetics, and Mechanistic Boundaries

4.1 Chemistry and disposition

D-mannose is a C-2 epimer of D-glucose, present at trace levels in several fruits including cranberry, and is produced for nutraceutical use by acid or enzymatic hydrolysis of plant polysaccharides or by yeast fermentation. After oral ingestion, the bulk of an oral dose is phosphorylated by hexokinase to mannose-6-phosphate; a small but biologically important fraction enters the systemic circulation unchanged and is filtered into urine [19,35,44]. Scaglione and colleagues' 2021 *Frontiers in Pharmacology* mechanistic review reported that D-mannose has a plasma half-life ranging from 30 minutes to several hours, that the large fraction is excreted unchanged into urine within 30–60 minutes, with the remainder within eight hours, and that no significant increase in blood glucose occurs during this time [35]. The 2023 European-Latin-Network Delphi consensus on regulatory classification [19] quantified that roughly 20–35 % of an excess D-mannose dose infiltrates the urine from the bloodstream within an hour. Cusumano *et al.* [6] demonstrated that a structurally analogous high-affinity FimH antagonist, when given orally, yielded three times higher urinary concentrations than the intraperitoneal dose at eight hours after administration, and that 95 % of the drug was excreted in urine unchanged. Hayashi *et al.* [45] extended these principles into a 2025 human pilot study of 1-deoxymannose, the closest D-mannose chemical analogue that retains FimH binding.

4.2 Mechanistic boundaries

D-mannose is not an antimicrobial. Scribano *et al.* [34] demonstrated that *in vitro* exposure to D-mannose does not select for stable FimH resistance mutations, in contrast to sub-inhibitory antibiotic exposure, which does. The pharmacology is therefore confined to recolonisation prevention, with the operative variables being urinary concentration at the moment of UPEC exposure, duration of coverage, and the proportion of infecting isolates that are type-1 fimbriated. D-mannose trials have not consistently stratified populations by FimH status, leaving open the question of whether non-response in 2024–2026 trials reflects populations whose recurrent isolates are predominantly PapG-dependent or non-fimbriated.

4.3 Dose–exposure relationship and the sub-clinical-dose gap

Clinically trialled doses cluster around 1–2 g/day in divided doses [1,20,21,36,39]. The disposition profile described by Scaglione *et al.* [19,35] implies that at single 500-mg doses — i.e., the minimum dose for any viable combination formulation — peak urinary D-mannose concentration is approximately one-quarter that of the 2 g/day trial dose, and *no controlled trial has examined a sub-1 g/day dose head-to-head against the 2 g/day dose*. This dose gap is the single most important constraint on the defensible clinical positioning of any low-dose mannose-containing formulation.

5. Phytochemistry and Quality Determinants of *Vaccinium macrocarpon*

5.1 Botanical identity and matrix complexity

V. macrocarpon Aiton is a low-trailing evergreen shrub cultivated principally in Wisconsin, Massachusetts, New Jersey, Oregon, Québec, and the Canadian Atlantic provinces. Its fruit is a heterogeneous matrix of organic acids (predominantly citric, malic, and quinic), simple sugars, soluble and insoluble fibre, micronutrients, and a polyphenolic fraction localised mainly in peel and seeds [16,17,48]. Processing decisions alter the polyphenol fingerprint substantially: juice products partition polyphenols into an aqueous phase and lose skin/seed-localised PACs, whereas whole-fruit powder products retain the matrix-original distribution of A-type PACs, anthocyanins, flavonols, and hydroxycinnamic acids [17,18]. This matrix dependence explains much of the heterogeneity among cranberry RCTs: trials using juice at sub-

anti-adhesion PAC doses have returned null findings [49], whereas recent trials using whole-fruit powder or PAC-standardised extracts have consistently shown benefit [5,50].

5.2 Bioactive constituents

1. **A-type proanthocyanidins** — oligomers and polymers of catechin/epicatechin linked predominantly through A-type bonds, the linkage type that confers the anti-adhesion phenotype against P-fimbriated UPEC [16,17]. Two principal analytical methods quantify total PACs: the 4-dimethylaminocinnamaldehyde assay and the European Pharmacopoeia method 2.8.14. The two assays are not interchangeable, and reported milligram values are method-dependent [16,17].
2. **Anthocyanins and flavonols** — cyanidin-3-galactoside, peonidin-3-galactoside, quercetin-3-galactoside, and myricetin glycosides. These contribute to antioxidant capacity, inhibition of low-density lipoprotein oxidation, and upregulation of endothelial nitric-oxide synthase signalling [16,23,24].
3. **Hydroxycinnamic and hydroxybenzoic acids** — caffeoylquinic, ferulic, *p*-coumaric acids; free and conjugated hydroxybenzoic acids; triterpenoids such as ursolic acid. Several appear in plasma 1–4 h after cranberry ingestion and have been statistically associated with acute FMD responses [23,24].
4. **Organic acids and minor sugars** — quinic, malic, citric, and trace D-mannose and D-fructose. These contribute to the sensory and tolerance profile of cranberry juices and may shape the gastrointestinal tolerability of combination products [16].

Table T1: Comparative Profile of the Two Actives

Attribute	Cranberry (*V. macrocarpon*)	D-Mannose	Source
Class	Polyphenol-rich fruit extract	C-2 epimer of D-glucose	[16,35]
Pharmacological target	PapG–globoside adhesion; secondary type-1 fimbrial modulation	FimH–uroplakin-Ia adhesion (type-1 fimbriated UPEC)	[7,9,17,34]
Daily clinically trialled dose	36 mg/day BL-DMAC PACs (~300 mL/day juice); 500 mg/day whole-fruit powder	1–2 g/day	[1,5,36,39,51]
Effect on rUTI in target populations	Significant reduction (RR 0.48–0.77 across meta-analyses and Stonehouse 2025)	Non-significant pooled effect at 2 g/day in 2024–2026 meta-analyses; possible benefit in FimH-positive subsets	[2,4,5,20,21,47]
Antioxidant / vascular effect	Modest FMD improvement; 24-h ambulatory DBP −2 mmHg in pre-hypertensive adults	None documented	[23–26]
Standardisation requirement	BL-DMAC or EP 2.8.14 PAC disclosure; A-type linkage profile; chemical fingerprint by HPLC-MS	HPLC enantiomeric purity; low D-glucose contamination; ICH stability	[16–18]
Tolerability	Favourable; sugar-load caution in metabolic syndrome; oxalate caution in stone formers	Favourable; mild gastrointestinal intolerance at 2 g/day minimised by titration	[20,44,52]
Regulatory status	EU: food / novel food; Pacran® claim negative at EFSA [41]	EU: food supplement; US: dietary supplement; India: FSSAI nutraceutical	[19,40–42]
6-month UK cost	Cranberry £55.95	D-mannose £158.40	[31]

5.3 Standardisation discipline

Colletti *et al.* [18] emphasised that the PAC-extraction process, drying method, solvent choice, and downstream blending into phospholipid carriers markedly affect oral bioavailability and the dose needed for a given urinary anti-adhesion signal. The 2026 Scaglione narrative review of phospholipid-formulated

cranberry [53] advanced the position that delivery technology can lower the effective polyphenol dose required. Adopting BL-DMAC with EP 2.8.14 cross-validation, declaring cultivar and harvest region, and providing a chemical fingerprint by HPLC-MS should be regarded as the minimum standardisation discipline for an evidence-aligned cranberry ingredient.

6. Bacterial Adhesion as the Pharmacological Target

The pathogenesis of uncomplicated cystitis and pyelonephritis is the stepwise adhesion cascade described in Section 3. Cusumano *et al.* [6] noted that acute infections begin when UPEC use type 1 pili tipped with FimH to bind mannosylated receptors on the luminal surface of bladder epithelial cells, and that bacteria aggregate in a type-1 pilus-dependent manner to form a clonal intracellular bacterial community. The multiple fimbrial and non-fimbrial adhesins coexisting in any UPEC population are the molecular reason a combination product covering FimH and PapG simultaneously is mechanistically defensible.

The Hung *et al.* [7] FimH crystal structure defines a deep, highly conserved pocket whose mannose-contacting residues are invariant across diverse UPEC strains, explaining why free urinary D-mannose competes with mannosylated uroplakin-Ia [10,34]. The Sarshar 2020 review [9] catalogues FimH as a validated pharmacological target. Wellens *et al.* [8] resolved the oligomannose-3–FimH structure and identified a series of high-affinity FimH antagonists that displace bacteria from uroepithelial cells *in vitro* and obstruct bladder colonisation in murine models. Cusumano *et al.* [6] extended the principle to orally administered FimH antagonists with high urinary recovery.

7. Mechanistic Basis of D-Mannose Anti-Adhesion Activity

The mechanism is competitive inhibition of the FimH lectin domain by free urinary D-mannose: the small molecule occupies the binding pocket of surface-displayed FimH on type-1-fimbriated UPEC, reducing the proportion of bacteria that engage uroplakin-Ia with sufficient shear-resistance to remain bound to uroepithelium, and thereby increasing the probability that voiding clears bacteria before tissue invasion can occur [7,34,35]. The pathway runs ingestion → partial absorption → partial urinary excretion → FimH occupancy → displacement of type-1-fimbriated bacteria → urinary voiding, and it acts *before* invasion events; once bacteria are intracellular, neither urinary D-mannose nor cranberry PACs can displace them.

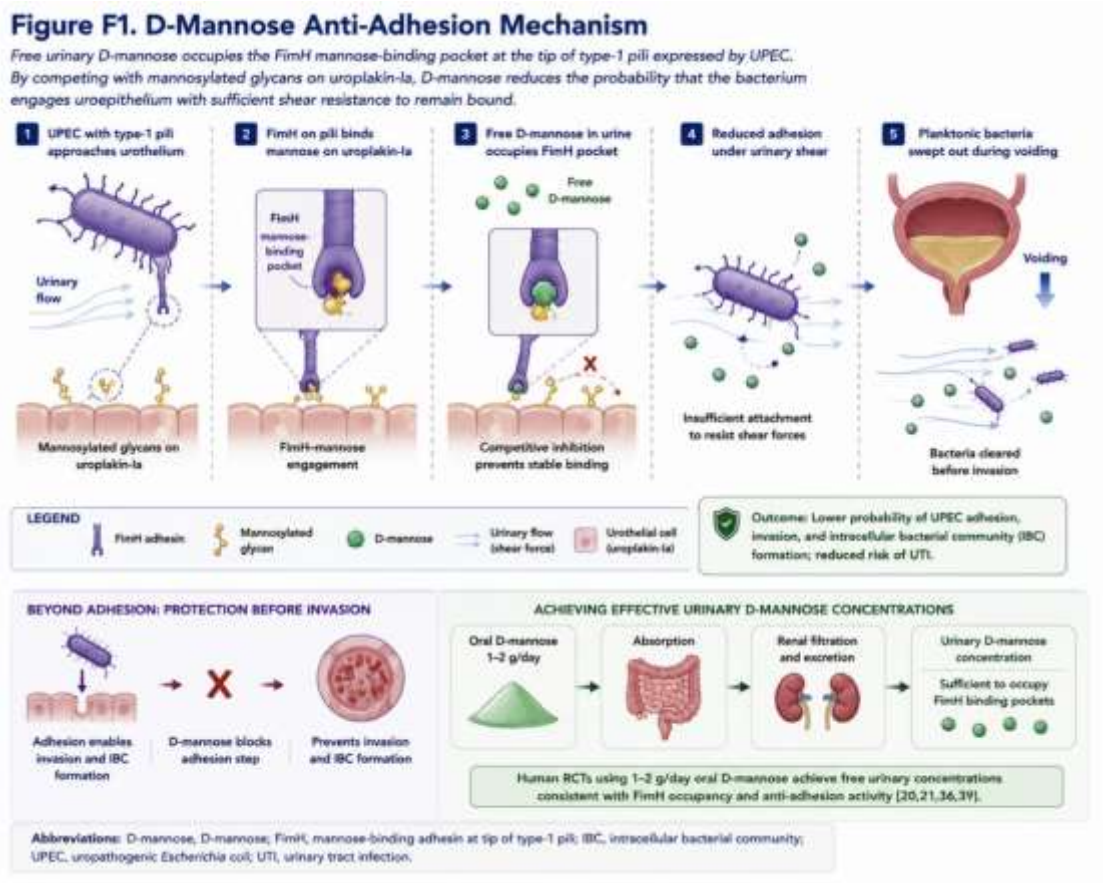

Figure F1: D-Mannose Anti-Adhesion Mechanism: Free urinary D-mannose occupies the FimH mannose-binding pocket at the tip of type-1 pili expressed by UPEC. By competing with mannosylated glycans on uroplakin-Ia, D-mannose reduces the probability that the bacterium engages uroepithelium with sufficient shear resistance to remain bound. Planktonic bacteria are then swept out of the bladder by voiding before invasion and IBC formation. The mechanism requires urinary concentrations of free mannose achievable with 1–2 g/day oral dosing regimens [20,21,36,39].

Kalas *et al.* [10] in 2017 characterised the FimH conformational ensemble as a catch-bond — binding is reinforced, rather than weakened, by shear — which enhances the importance of occupying the binding pocket before the bacterium engages uroepithelium under flow. Scribano *et al.* [34] demonstrated that exposure of UPEC to D-mannose does not select for stable FimH mutations or reduce FimH-binding-pocket integrity. The catch-bond and absence-of-resistance-selection frameworks together explain why long-term D-mannose prophylaxis does not impose the same resistance-selection penalty as long-term antibiotic prophylaxis [34].

8. Cranberry Anti-Adhesion and Complementarity with D-Mannose

Cranberry A-type PACs and their colonic-microbiota-derived metabolites block P-fimbrial adhesion and modulate type-1 fimbrial adhesion through multiple chemical layers [16,17,54]. Liu *et al.* [54] showed in a randomised, double-blind, placebo-controlled pilot that consumption of cranberry chews produced urinary anti-adhesion activity against both P-type *E. coli* and type-1 *E. coli* in healthy volunteers. EFSA and FDA both agree that the mechanism by which cranberry PACs contribute to UTI prevention involves P-fimbrial binding inhibition [40–43]. The 2025 EFSA Pacran® opinion [41] concluded that the evidence is insufficient to establish a cause-and-effect relationship. The 2020 FDA enforcement-discretion letter [43] acknowledged "limited and inconsistent scientific evidence" for cranberry juice beverages (≥ 27 % juice at 8 oz/day) and "limited scientific evidence" for cranberry dietary supplements (≥ 500 mg cranberry powder). These regulatory observations delimit what is legally claimable, irrespective of mechanistic conviction.

The complementarity of cranberry PACs and D-mannose is therefore evidence-based but unsettled in regulatory adjudication. Cranberry targets the PapG–globoside axis primarily; D-mannose targets the FimH–mannose axis. The two actives together should cover a wider range of clinical UPEC isolates than either alone, but no adequately powered trial has demonstrated additive efficacy to date.

9. Clinical Evidence for D-Mannose in Recurrent UTI

9.1 Early favourable signals

Porru *et al.* [36] reported a mean time to UTI recurrence of 52.7 days with antibiotic treatment and 200 days with oral D-mannose ($p < 0.0001$) in a 60-woman cross-over design, with significant decreases in bladder pain, urinary urgency, and 24-hour voiding frequency. Lenger *et al.* [55] in a 2020 systematic review and meta-analysis of seven RCTs (n = 598 in the key comparison) reported D-mannose was protective against recurrent UTI compared with placebo (RR 0.23, 95 % CI 0.14–0.37).

9.2 The 2024 *JAMA Internal Medicine* trial and meta-analytic confirmation

Hayward *et al.* [4] conducted a 2024 *JAMA Internal Medicine* RCT in which women with recurrent UTI in primary care received D-mannose 2 g daily or placebo for six months. Medically attended, clinically suspected UTI occurred in approximately 51 % of the D-mannose group and 56 % of the placebo group — a non-significant difference. Three subsequent meta-analyses incorporated this trial:

- Vargas *et al.* [21] synthesised the available D-mannose RCTs in rUTI populations and reported results consistent with the Hayward null finding, with substantial heterogeneity.
- Murali Krishna *et al.* [20] reported a non-significant pooled RR; the non-significant pooled adverse-event risk was RR 0.81 (95 % CI 0.09–6.91).
- Al-Hajjaj *et al.* [22] reported a pooled RR of 0.37 (95 % CI 0.11–1.30) with very high heterogeneity ($I^2 \approx 94$ %).
- Cooper *et al.* [1] in the 2022 Cochrane review judged the certainty of evidence to be low for the prevention outcome, citing heterogeneity and the absence of standardised dosing regimens.

9.3 Wagenlehner non-inferiority against fosfomycin

Wagenlehner *et al.* [39] conducted a randomised, double-blind, non-inferiority pilot in acute uncomplicated cystitis comparing 2 g/day D-mannose with fosfomycin. The investigators reported that D-mannose was

non-inferior to fosfomycin in post hoc analyses (recurrence rates of 13.2 % vs 13.3%, respectively) with markedly fewer gastrointestinal adverse events (9.8 % vs 24.6 %).

9.4 Interpretation for product development

Three practical implications follow for combination-product development with sub-trial D-mannose doses. First, the value proposition of a combination product depends on synergy with another mechanistically complementary active or on a co-administered behavioural intervention (hydration, post-coital voiding) that increases the probability of UPEC clearance before adhesion. Second, individual RCT variability is consistent with responder subsets, particularly women whose recurrent isolates are predominantly type-1 fimbriated; future trials should be biomarker-stratified. Third, the safety and tolerability profile remains a competitive advantage, with non-significant pooled adverse-event rates comparable to placebo [20].

10. Clinical Evidence for Cranberry in UTI Prevention

The cranberry evidence base is the most extensive of any non-antibiotic rUTI prophylactic. The 2023 Williams *et al.* Cochrane update [2] — the seventh iteration of CD001321 — synthesised 50 RCTs and 8 857 participants and concluded that cranberry products reduce the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs, in children, and in people susceptible to UTIs following interventions, while explicitly noting that the available evidence does not support cranberry use in the elderly, patients with bladder-emptying problems, or pregnant women.

Maki *et al.* [38] showed in a 24-week, double-blind, placebo-controlled design with 480 mL/day low-calorie cranberry juice in 373 women with recent UTI a significant cumulative reduction in clinical UTI episodes. Fu *et al.* [47] in a 2017 meta-analysis reported that cranberry reduced the risk of rUTI by 23 % (pooled RR 0.77; 95 % CI 0.64–0.93). Moro *et al.* [56] conducted a 2024 network meta-analysis in *European Urology Focus* that reaffirmed the urinary-reduction signal but qualified between-format comparisons. Babar *et al.* [50] in a head-to-head comparison of 37 mg/day PAC cranberry extract versus a 2 mg/day low-PAC comparator over six months in 148 women, reported that the proportion experiencing more than one UTI was significantly lower in the active cranberry group (10.8 % vs 25.8 %, $p = 0.04$). Vostálová *et al.* [57] earlier reported a near-identical signal at 500 mg/day cranberry fruit powder standardised to 0.56 % PACs in 182 women with at least two UTIs in the preceding year.

Stonehouse *et al.* [5] published the most rigorous recent RCT in 2025: a six-month, multicentre, double-blind, placebo-controlled trial of 500 mg/day Swisse High Strength Cranberry (Pacran®) whole-fruit powder in 150 women with rUTI history. The active arm reduced culture-confirmed UTI by 52 % (adjusted RR 0.48, 95 % CI 0.26–0.87; $p = 0.01$), reduced *E. coli* UTI specifically (RR 0.49, 95 % CI 0.24–1.01; $p = 0.05$), substantially reduced UTI with urinary frequency and urgency (RR 0.29, 95 % CI 0.13–0.63; $p < 0.01$), delayed time to first UTI (hazard ratio 0.36, 95 % CI 0.18–0.74; $p = 0.01$), and reduced mean total UTIs per participant (incidence RR 0.41, 95 % CI 0.21–0.79; $p = 0.01$) without safety concerns [5].

The Barbosa-Cesnik *et al.* [49] trial of 8 oz of 27 % cranberry juice twice daily in college women — a low-dose, low-PAC regimen — failed to demonstrate a 6-month reduction in recurrence; this is the canonical cautionary tale about dose and matrix.

Table T2: Summary of Principal Human Studies (2014–2026)

Study	Year	Design	Population	Intervention	n	Key result
Maki [38]	2016	RCT double-blind	Women with recent UTI	480 mL/day low-calorie cranberry juice vs placebo	373	Reduced clinical UTI episodes
Fu [47]	2017	Meta-analysis	Healthy women with rUTI	Cranberry products vs placebo/control	1 498 (7 RCTs)	Pooled RR 0.77 (0.64–0.93)
Koradia [28]	2019	RCT double-blind pilot	Pre-menopausal women with rUTI	Probiotic + cranberry (36 mg/day PACs) vs placebo	90	rUTI 9.1 % vs 33.3 % ($p = 0.0053$)
Murina [27]	2020	Open-label prophylaxis pilot	Pre-menopausal women with rUTI	LC11 + cranberry + D-mannose	55	Effective and safe in combination

Rădulescu [29]	2020	RCT, acute therapy	Non-pregnant women with uncomplicated lower UTI	1 g/day D-mannose + 400 mg cranberry + TMP-SMX vs TMP-SMX alone	93	Combination feasible, safe
Babar [50]	2021	RCT double-blind	Women with rUTI	37 mg/day vs 2 mg/day PAC extract	148	10.8 % vs 25.8 % (p = 0.04)
Harding ALTAR [3]	2022	RCT non-inferiority	rUTI women	Methenamine hippurate vs low-dose antibiotic	n large	Methenamine non-inferior to antibiotic
Wagenlehner narrative [37]	2022	Narrative review	rUTI	D-mannose clinical context	—	Mechanistic rationale, early signals
Cooper [1]	2022	Cochrane review	rUTI women	D-mannose vs placebo	multiple RCTs	Low certainty for prevention
Williams [2]	2023	Cochrane review	rUTI, children, post-intervention	Cranberry vs placebo/control	8 857 (50 RCTs)	Reduced in targeted populations
Hayward [4]	2024	RCT placebo-controlled	Women with rUTI	D-mannose 2 g/day vs placebo	598	No statistically significant advantage
Moro [56]	2024	Network meta-analysis	rUTI across populations	Cranberry juice/tablets/liquids vs comparators	3 091 (20 RCTs)	Cranberry juice −54 % vs no treatment
Vargas [21]	2025	Meta-analysis	rUTI women	D-mannose vs control/antibiotic	Multiple RCTs	Non-significant
Murali Krishna [20]	2025	Meta-analysis	Adult women with rUTI	D-mannose vs placebo/no treatment	890 (4 RCTs)	RR non-significant
Stonehouse [5]	2025	RCT double-blind	Women with rUTI	500 mg/day whole cranberry fruit powder vs placebo	150	RR 0.48 (0.26–0.87)
Wagenlehner [39]	2025	RCT double-blind	Acute uncomplicated cystitis	D-mannose vs fosfomycin	111	Non-inferiority post hoc
Al-Hajjaj [22]	2026	Meta-analysis	Women with rUTI	D-mannose monotherapy vs comparators	1 038	RR 0.37 (0.11–1.30); I^2 = 94 %
Joshi [31]	2025	Health-economics	UK NHS pricing	Non-antimicrobials vs antimicrobials	—	Cranberry £55.95; D-mannose £158.40

11. Evidence for Cranberry–D-Mannose Combinations

Combination evidence remains smaller. Rădulescu *et al.* [29] randomised 93 non-pregnant Romanian women aged 18–60 with acute uncomplicated lower UTI to 1 g/day D-mannose + 400 mg cranberry extract plus trimethoprim–sulfamethoxazole for seven days, or TMP-SMX alone for seven days; the study demonstrated feasibility and safety. Murina *et al.* [27] reported on an orally administered combination of *Lactobacillus paracasei* LC11 + cranberry + D-mannose (Lactoflorene Cist®) in pre-menopausal women with rUTI, concluding that prophylactic treatment was effective and safe. Koradia *et al.* [28] tested a probiotic + cranberry combination (Bio-Kult Pro-Cyan, 36 mg/day PACs) in 90 pre-menopausal women with rUTI over 26 weeks: rUTI incidence 9.1 % vs 33.3 % on placebo (p = 0.0053); time to first UTI 174 vs 90 days (p = 0.001); duration of UTI 5 vs 12 days (p = 0.009); and antibiotic courses used 3 vs 11 ($p < 0.05$).

The Venturini *et al.* [58] non-RCT bundle-of-care study of 47 women combining behavioural strategies, probiotics, D-mannose, and cranberry demonstrated a 76 % reduction in urinary infections (p <

0.001) and a reduction in overall antibiotic exposure of more than 90 % ($p < 0.001$), with 80.5 % of women reporting improvement in quality of life and 87.2 % adherence. The 2025 Maharani *et al.* [59] network meta-analysis ranked combinations of *Lactobacillus*, cranberry, and D-mannose as having the lowest adverse-effect burden of all preventive strategies.

12. Microbiome Consequences: The Urobiome and Beyond

The historical paradigm of a sterile bladder has been overturned: the urinary tract of healthy individuals hosts a diverse urobiome dominated by *Lactobacillus*, *Gardnerella*, *Streptococcus*, and *Corynebacterium* in women, with reduced diversity in women with recurrent UTI. Beerepoot and Geerlings [33] documented that vaginal oestrogen in postmenopausal women restores the *Lactobacillus* flora and reduces vaginal Enterobacteriaceae carriage, with downstream effects on rUTI.

A 2025 editorial commentary by González [60] reviewed a randomised, double-blind, placebo-controlled crossover study of cranberry juice on the urobiome of healthy adults and observed that cranberry consumption can significantly modulate urobiome composition, with changes that likely reflect broader shifts in the interconnected gut and vaginal microbiota, and a trend toward decreased *Lactobacillus* in healthy women. While the *Lactobacillus* depletion did not survive multiple-comparison correction in the underlying trial, the sex-specificity underscores the need for menopausal-status stratification in future cranberry RCTs [60].

D-mannose is not reported to produce specific gut-microbiome shifts. Cranberry (poly)phenols are extensively metabolised by colonic microbiota to lower-molecular-weight derivatives that drive much of the systemic pharmacology. Plausible reductions in cumulative antibiotic exposure in combination users — Koradia *et al.* [28] documented 3 vs 11 antibiotic courses in active vs placebo — should translate to reduced resistome selection pressure, although this remains to be measured directly.

13. Antioxidant Activity of Cranberry Polyphenols

Cranberry (poly) phenols contribute antioxidant capacity through both direct radical-scavenging activity of parent aglycones and induction of phase-II and endogenous antioxidant enzymes. Basu *et al.* [52] demonstrated in metabolic-syndrome women that low-calorie cranberry juice increased plasma antioxidant capacity and decreased lipid-oxidation biomarkers. Nemzer *et al.* [16] mapped compositional and antioxidant activity of cranberry products, showing that PAC content by BL-DMAC correlated strongly with ferric-reducing antioxidant power and oxygen radical absorbance capacity.

14. Endothelial and Vascular Effects of Cranberry Polyphenols

Vascular benefit derives from a discrete set of cranberry (poly)phenol metabolites whose plasma kinetics have been characterised. Dohadwala *et al.* [24] demonstrated in 44 coronary-artery-disease subjects that 4 weeks of cranberry juice (480 mL/day) yielded a favourable effect on carotid-femoral pulse wave velocity: central aortic stiffness decreased after cranberry juice (8.3 ± 2.3 to 7.8 ± 2.2 m/s) in contrast with an increase after placebo (8.0 ± 2.0 to 8.4 ± 2.8 m/s) ($P = 0.003$), and an acute-improvement signal of FMD (7.7 ± 2.9 % to 8.7 ± 3.1 %, $P = 0.01$) and digital peripheral arterial tonometry (0.10 ± 0.12 to 0.23 ± 0.16, $P = 0.001$) at 4 h.

15. Cranberry and Blood-Pressure Regulation

The blood-pressure evidence is heterogeneous and broadly neutral on systolic blood pressure, but suggestive for DBP and 24-h ambulatory pressure. Richter *et al.* [23] in a randomised crossover trial of 40 adults with overweight/obesity and elevated brachial BP (mean 124 ± 2 / 81 ± 1 mmHg) tested cranberry juice (500 mL/day, 27 % juice) versus matched placebo over two 8-week periods: cranberry significantly reduced 24-h diastolic ambulatory BP by approximately 2 mm Hg compared to placebo ($p = 0.05$) during daytime hours, with a marked change in LDL profile (large LDL-C particle concentration +29.5 vs −6.7 nmol/L, $p = 0.02$; LDL size +0.073 vs −0.068 nm, $p = 0.001$). Central SBP did not change significantly.

Wang *et al.* [25] in a subgroup analysis of cranberry juice (mean 432 mL/day, 8 weeks, 149 participants), found significantly decreased SBP and DBP by 1.52 mmHg each. Pourmasoumi *et al.* [26] reported directional SBP/DBP reduction without statistical significance in pooled cardiometabolic-risk RCTs. The 2026 Bahreyni *et al.* [46] meta-analysis of 12 cranberry RCTs concluded that cranberry did not significantly change systolic or diastolic BP overall, although favourable signals appeared in juice-based, shorter, or younger-participant subgroups. The pressure signal therefore concentrates in (i) diastolic ambulatory pressure in pre-hypertensive subjects [23], (ii) populations with elevated baseline

oxidative stress or inflammation, and (iii) sustained dosing above approximately 450 mL/day juice equivalents or 500 mg/day of PAC-standardised whole-fruit powder.

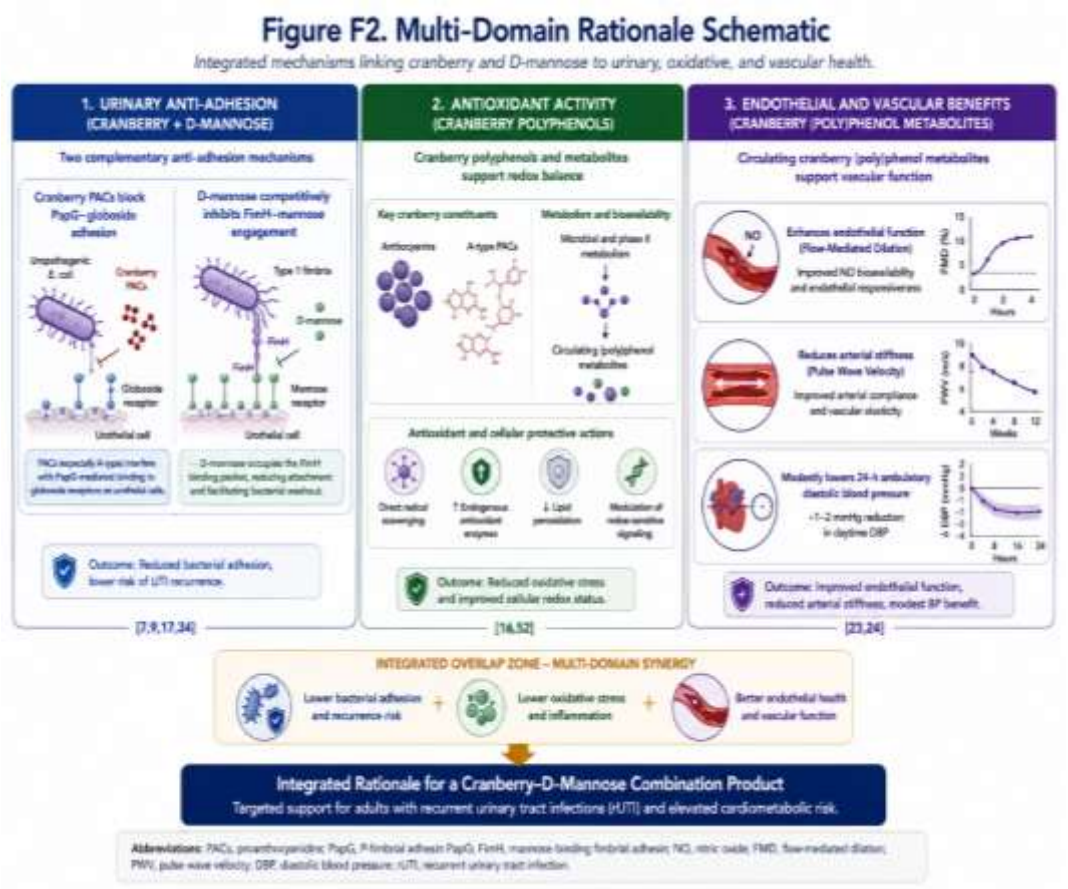

Fig F2: Multi-Domain Rationale Schematic: A three-column schematic showing: (i) urinary anti-adhesion by cranberry + D-mannose, covering PapG–globoside (cranberry PACs) and FimH–mannose engagement [7,9,17,34]; (ii) antioxidant activity from cranberry anthocyanins and PAC-derived metabolites [16,52]; (iii) endothelial and vascular benefits from circulating cranberry (poly)phenol metabolites enhancing FMD, reducing pulse wave velocity, and modestly lowering 24-h ambulatory diastolic blood pressure [23,24]. The overlap zone is the integrated rationale for a cranberry–D-mannose combination product in adults with rUTI and elevated cardiometabolic risk.

16. Pharmacoeconomics — Comparative Costs of Non-Antibiotic Prophylaxes

Joshi *et al.* [31] in a 2025 UK cost comparison computed the median cost of six months of prophylactic treatment with five non-antimicrobial options and four antimicrobial comparators. Non-antimicrobial costs: vaginal oestrogen £22.04; cranberry £55.95; methenamine hippurate £100.44; probiotics £139.50; D-mannose £158.40. Antimicrobial prophylaxis costs: trimethoprim £5.08; cefalexin £7.97; amoxicillin £10.71; nitrofurantoin £16.32. The authors noted that antimicrobial management options for the prophylaxis of UTIs were found to be generally cheaper across the board, in comparison to non-antimicrobial products, but emphasised that the continuing public-health crisis about over-prescribing of antimicrobials makes non-antimicrobials an ever-important consideration [31].

Stamm *et al.* [30] in the foundational 1981 cost-effectiveness analysis of antimicrobial prophylaxis, showed that in women with three UTIs per year, the annual cost of prophylaxis ($85.82) was less than treatment of acute episodes ($392.30), and that prophylaxis became cost-effective when charges per episode exceeded $42.00. Eells *et al* [32] in a 2013 Markov Monte Carlo analysis of five prevention strategies reported that daily antibiotic use was the most effective rUTI strategy against daily cranberry pills, daily oestrogen, and acupuncture, with cost savings and quality-adjusted life-year improvements for most regimens.

Table T3: Six-Month Prophylaxis Cost Comparison

Strategy	Class	6-month median cost (UK £)
Vaginal oestrogen	Non-antimicrobial	£22.04
Cranberry	Non-antimicrobial	£55.95
Methenamine hippurate	Non-antimicrobial	£100.44
Probiotics	Non-antimicrobial	£139.50
D-mannose	Non-antimicrobial	£158.40
Trimethoprim	Antimicrobial	£5.08
Cefalexin	Antimicrobial	£7.97
Amoxicillin	Antimicrobial	£10.71
Nitrofurantoin	Antimicrobial	£16.32

Source: [31]

17. Comparative Effectiveness of Non-Antibiotic Prophylactic Strategies

Methenamine hippurate is supported by the 2022 Harding ALTAR RCT [3] demonstrating non-inferiority to low-dose antibiotic prophylaxis. The 2026 Juliebø-Jones *et al.* [61] Norwegian prescribing-trend analysis showed methenamine hippurate prescribing stable through 2020 followed by expansion after Harding ALTAR. Vaginal oestrogen in postmenopausal women restores the *Lactobacillus* flora, reduces vaginal Enterobacteriaceae carriage, and reduces rUTI compared with placebo [33]. Cranberry products reduce rUTI in women with recurrent infection, in children, and in post-intervention patients, with the 2023 Cochrane review [2] confirming the benefit and the 2025 Stonehouse RCT [5] confirming the per-protocol 52 % culture-confirmed reduction. FimH antagonists of medicinal-chemistry origin [6] produce high-affinity anti-adhesion in murine models with complete urinary recovery of intact drug but have not yet advanced to phase III trials in uncomplicated UTI.

18. The Biotex Life Solutions Combination Product

18.1 Product description

Fig F3: Photograph of the Biotex Life Solutions cranberry + D-mannose product. Per serving: D-mannose 500 mg + Vaccinium macrocarpon fruit 10 mg.

The Biotex Life Solutions product is a daily-use cranberry + D-mannose combination delivering, **per serving:**

- **D-mannose 500 mg**
- ***Vaccinium macrocarpon* fruit 10 mg**

Both actives are presented at sub-clinical single-component doses relative to the positive RCT evidence base (1–2 g/day D-mannose [1,36,39] and 36 mg/day BL-DMAC PACs or 500 mg/day whole-fruit powder cranberry [5,50,57]).

18.2 Mechanistic rationale

The combination has a dual mechanistic rationale. At the urinary-tract interface, cranberry A-type PACs and D-mannose act on distinct, mutually non-redundant molecular targets of UPEC adhesion — PapG–globoside and FimH–uroplakin-Ia, respectively — theoretically superior to either component alone for the polyclonal UPEC populations encountered in rUTI. The clinical positioning is therefore adhesion-directed: the formulation acts as a bladder-surface anti-adherence product, reducing the probability that adhesion events initiate new infections.

At the vascular interface, cranberry (poly)phenol metabolites produced by colonic microbiota act on the vascular endothelium to improve flow-mediated dilation acutely and over one month of daily consumption, to reduce central arterial stiffness over four weeks [24], and to produce a modest 24-h ambulatory diastolic blood pressure reduction in pre-hypertensive adults [23]. This secondary benefit is mechanistically separable from the urinary effect but is delivered to the same end-user — most often an adult woman taking long-term prophylaxis — and is the basis of the cautious vascular claims summarised in Table T4.

18.3 Honest evidence-strength summary

- **Strongest evidence:** cranberry PAC-standardised products reducing culture-confirmed UTI in women with rUTI [2,5,47].
- **Moderate evidence:** cranberry polyphenols improving FMD and one-month endothelial function [23,24]; cranberry juice reducing 24-h ambulatory DBP in pre-hypertensive adults [23].
- **Mixed evidence:** D-mannose monotherapy for rUTI prophylaxis [4,20,21]; cranberry for systolic BP reduction [25,26]; cranberry–D-mannose combinations on culture-confirmed outcomes [27–29].
- **Insufficient evidence for the present formulation:** D-mannose at sub-1 g doses for prophylactic efficacy; any specific ratio of cranberry: D-mannose as synergistically optimal; long-term microbiome preservation in combination users.

18.4 Integrated positioning

Cranberry + D-mannose together restore two lost anti-adhesion barriers of the uroepithelium, with cranberry polyphenols additionally conferring an effect on endothelial function that can be communicated within the boundaries of the available evidence. The product is supported by adequate hydration (≥ 1.5 L/day water), post-coital voiding, and avoidance of unnecessary antibiotic courses [3,19,33]. The product's per-serving exposure — D-mannose 500 mg and cranberry fruit 10 mg — sits below published single-component positive-RCT dose levels; the most defensible positioning strategy therefore pairs **mechanistically informed communication** (anti-adhesion + vascular polyphenols) with **lifestyle co-administration** (hydration, post-coital voiding) and **product-specific clinical validation** over time.

19. Formulation, Dosing, and Standardisation

19.1 Dose context relative to the evidence

The clinically demonstrated effective cranberry dose range for UTI prevention is anchored around 36 mg/day BL-DMAC PACs (~300 mL/day standard cranberry juice cocktail). PAC-standardised extracts have been trialled at 37 mg/day across daily divided doses [50], and whole-fruit powder products delivering 500 mg/day of powder (≥ 0.56 % PACs by BL-DMAC) have been trialled with positive results [5,57]. For D-mannose, the doses in clinical trials range from 1 g/day [36,51] to 2 g/day [36,39], with pooled meta-analytic RCTs clustering near 2 g/day [20,21]. Reasonable monotherapy-equivalent dose targets for a combination product are cranberry delivering ≥ 36 mg/day BL-DMAC PACs (500–1 000 mg/day whole-fruit powder) plus D-mannose 1–2 g/day.

Subclinical doses, such as the 500 mg D-mannose + 10 mg cranberry fruit composition of the present Biotex formulation, should be acknowledged transparently. The honest expectation is that single-component clinical benefit cannot be inferred by direct dose translation of trial outcomes, and ADME-aligned delivery enhancements (e.g., phospholipid-formulated cranberry per Scaglione 2026 [53]) are an active area of development.

Table T4: Defensible vs Impermissible Claims for Combination Products

Defensible claims (evidence-supported)	Impermissible claims (not evidence-supported)

Cranberry polyphenols deliver anti-adhesion activity in human urine (ex vivo studies) [54]	Cures or treats active cystitis, pyelonephritis, or asymptomatic bacteriuria
Cranberry products reduce symptomatic, culture-verified UTIs in women with recurrent infection, in children, and in post-intervention populations [2,5]	Effective in patients with neurogenic bladder, indwelling catheters, or pregnancy
Cranberry polyphenols improve acute and sustained FMD and reduce central arterial stiffness [23,24]	Lowers blood pressure to a clinically meaningful degree in stage 2 hypertension
Sustained 24-h ambulatory DBP may improve modestly in pre-hypertensive users [23]	Replaces antibiotic prophylaxis for rUTI as monotherapy
Free urinary D-mannose competes for FimH on type-1-fimbriated UPEC, reducing in vitro adhesion [7,9,34]	D-mannose alone prevents recurrent UTI in unselected rUTI populations
D-mannose has a favourable tolerability profile comparable to placebo at the doses trialled [20,39]	Equivalent to antibiotic prophylaxis for rUTI as monotherapy
Cranberry + D-mannose combination is mechanistically rational and safer than long-term antibiotic prophylaxis [27–29,58]	Synergy is established in head-to-head combination RCTs (no such trial exists)

19.2 Cranberry standardisation requirements

Standardisation requirements for a defensible combination product include: (i) disclosure of PAC content by BL-DMAC or EP 2.8.14 — with method explicit, because the two assays are not interchangeable [16,17]; (ii) consistent A-type linkage profile verified by HPLC-MS; (iii) pesticide and heavy-metal residue compliance consistent with USP/EP nutraceutical monographs; (iv) batch-to-batch PAC reproducibility within a tight tolerance range; (v) avoidance of matrix components that suppress oral PAC absorption; (vi) transparent declaration of cultivar, growing region, harvest year, plant part, drying method, and extraction solvent [16–18].

19.3 D-mannose quality and dosage form

Quality-control criteria for a clinical-grade D-mannose include: HPLC-documented enantiomeric purity; absence of D-glucose contamination sufficient to compromise glycaemic tolerance in pre-diabetic consumers; absence of bacterial endotoxin above USP/EP limits; sieve mesh size and flow properties suitable for capsule/tablet direct compression; and process-related impurity profiling. Solid oral dosage forms deliver 500 mg or 1 g per unit and are typically titrated to a 1–2 g/day dose given with water once or twice daily. Stability testing should follow ICH Q1A(R2) for climatic zone III/IV.

20. Safety, Tolerability, and Precautions

The Hayward *et al.* 2024 D-mannose trial [4] did not report a statistically significant adverse-event excess over placebo. The Murali Krishna *et al.* 2025 [20] pooled risk ratio for any adverse event was 0.81 (95 % CI 0.09–6.91), non-significant. Gastrointestinal intolerance (loose stools, abdominal discomfort) is the most commonly reported adverse symptom at 2 g/day and is largely dose-related; titration to 1 g/day reduces the risk [35,44]. Wagenlehner *et al.* [39] reported gastrointestinal adverse events of 9.8 % for D-mannose vs 24.6 % for fosfomycin.

Cranberry products carry no demonstrated drug interactions of clinical significance at typical nutraceutical doses [43]. A theoretical interaction with warfarin via inhibition of CYP2C9-mediated metabolism has been raised by isolated case reports of INR elevation when very high daily volumes of cranberry juice (~1 L/day) are consumed; this is not a class effect of cranberry PACs and is not reported with PAC-standardised preparations. Cranberry increases urinary oxalate excretion modestly and may be inappropriate in oxalate-stone formers. Warnings include added-sugar exposure from sweetened juices in metabolic-syndrome, pre-diabetic, and insulin-resistant populations [16,52].

Contraindications to any nutraceutical urinary-tract agent include features of upper-tract or complicated infection — fever, flank pain, vomiting, visible haematuria, pregnancy, infection in a child or man, known kidney disease, diabetes with systemic symptoms, obstruction, or catheter-associated symptoms — since these may signal pyelonephritis requiring urgent antibiotic therapy and clinical assessment.

Table T5: Risk of Bias and GRADE Certainty of Principal RCTs

RCT (year)	Randomisation	Allocation concealment	Blinding	Incomplete outcome	GRADE certainty (per outcome)
Hayward [4] 2024	Low	Low	Low	Low	Moderate for 6-month rUTI recurrence
Stonehouse [5] 2025	Low	Low	Low	Low	High for 6-month culture-confirmed UTI
Maki [38] 2016	Low	Low	Low	Moderate	Moderate
Babar [50] 2021	Low	Low	Low	Low	Moderate for per-protocol
Koradia [28] 2019 (pilot)	Unclear	Unclear	Low	Moderate	Low (pilot, n = 90)
Wagenlehner [39] 2025	Low	Low	Low	Low	Low (pilot, post hoc primary)

21. Global Regulatory Landscape and Claim Substantiation

For FDA markets, the 2020 enforcement-discretion letter permits qualified health claims with explicit qualifiers: cranberry juice beverages (≥ 27 % juice at 8 oz/day) — "limited and inconsistent scientific evidence" for reduced risk of rUTI in healthy women; cranberry dietary supplements (≥ 500 mg cranberry powder) — "limited scientific evidence" [43]. EFSA's 2025 Pacran® opinion [41] concluded that the evidence is insufficient to establish cause and effect; the earlier 2014 EFSA opinion on Pacran® [40] reached a similar negative conclusion, and the 2011 EFSA opinion on cranberry PACs [42] rejected the claim for the same reason. Marketers must therefore adapt to a regime-specific claim framework.

D-mannose is regulated as a dietary supplement in the United States, as a food supplement in the European Union, and as a nutraceutical in India. The Scaglione *et al.* 2023 ELN-Delphi consensus [19] concluded that the regulatory classification of D-mannose products should follow the chemical identity of the active substance (a free monosaccharide), not the implied therapeutic claim of the labelling. The position directly affects claim admissibility: a product labelled as "D-mannose" cannot simultaneously be represented as a botanical extract, an antimicrobial, or a urinary antiseptic; it can be positioned within structure–function language reflecting its anti-adhesion mechanistic role.

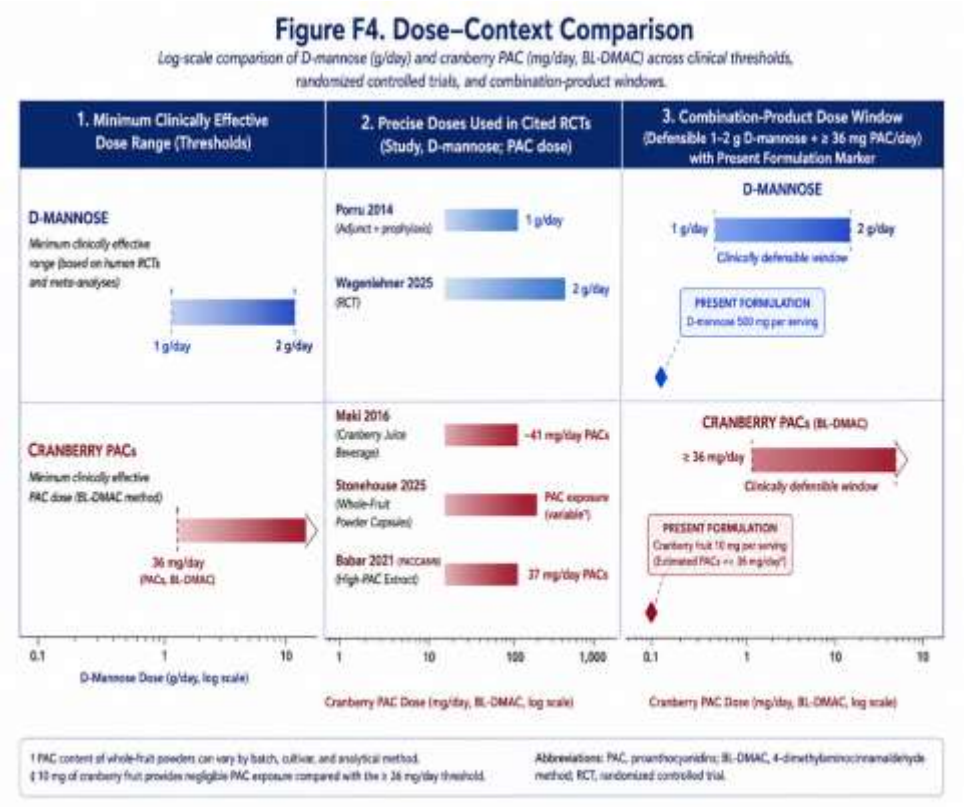

Fig F4: Dose-Context Comparison: A log-scale horizontal bar chart with three columns. Column 1: minimum clinically effective D-mannose dose range (1–2 g/day) and minimum clinically effective cranberry PAC dose (36 mg/day BL-DMAC). Column 2: precise doses used in cited RCTs — Porru 1 g [36]; Wagenlehner 2025 2 g [39]; Maki ~41 mg PACs [38]; Stonehouse whole-fruit powder PAC exposure [5]; Babar 37 mg PAC [50]. Column 3: combination-product dose window centred on the clinically defensible 1–2 g D-mannose + ≥ 36 mg/day PAC frame, with the present formulation marker (D-mannose 500 mg + cranberry fruit 10 mg per serving) overlaid to highlight the dose gap.

22. Evidence Gaps and Proposed Research Agenda

Five gaps warrant prioritisation. (i) A large, PAC-standardised, placebo-controlled RCT of cranberry + D-mannose combination prophylaxis in pre-menopausal and post-menopausal women stratified by baseline FimH-vs-PapG strain carriage [20]. (ii) Long-term (≥ 12 months) safety and microbiome effects of the combination, particularly on vaginal *Lactobacillus* recolonisation, urobiome composition, and gut resistome carriage, recognising the *Lactobacillus*-depletion signal reported by recent cranberry-urobiome trials [60]. (iii) A DBP / ambulatory-BP RCT in pre-hypertensive subjects using whole-fruit powder, with pre-specified mediation analysis on the hydroxycinnamic-acid metabolites. (iv) Co-formulation of cranberry PACs with phospholipids [53] or with *Lactobacillus paracasei* LC11 [27]; these delivery technologies require both efficacy endpoints (culture-confirmed UTI prevention) and adherence/acceptability outcomes. (v) Subgroup analyses in populations currently excluded: catheter-associated UTI, neurogenic bladder, post-menopausal urogenital atrophy, pregnancy, children, and populations with elevated comorbidity burden such as diabetes and chronic kidney disease. Pharmacoeconomic analyses using the Joshi *et al.* [31] methodology and the Harding *et al.* [3] non-inferiority framework would translate clinical outputs into adoption guidance.

23. Conclusion

Cranberry A-type proanthocyanidins and D-mannose target two complementary adhesin systems of uropathogenic *E. coli* — PapG and FimH, respectively — and have independent evidence bases for reducing the incidence of recurrent urinary tract infection and for improving selected markers of vascular health. The 2024 *JAMA Internal Medicine* D-mannose RCT [4] tempered expectations for D-mannose as monotherapy, with three 2025–2026 meta-analyses [20–22] failing to confirm a statistically significant prophylactic benefit at 2 g/day. In contrast, the 2023 Cochrane review [2] and the 2025 Stonehouse whole-fruit-powder RCT [5] have reinforced the urinary protective effect of cranberry at doses delivering ≥ 36 mg/day BL-DMAC PACs. The 2022 Harding ALTAR RCT [3] and the 2026 Norwegian prescribing-trend analysis [61] document a paradigm shift toward non-antibiotic prophylaxis. The 2025 Pacran® EFSA opinion [41] and the 2020 FDA qualified health-claim letter [43] define the regulatory boundary. The Biotex Life Solutions cranberry + D-mannose product (D-mannose 500 mg + *Vaccinium macrocarpon* fruit 10 mg per serving) positions both actives at their mechanistically distinct points of action, supplemented by cranberry (poly)phenol metabolites that act on the vascular endothelium [23,24]. Both actives are delivered at sub-clinical single-component dose ranges, and the per-day exposure is therefore best understood as a mechanistically rational adhesion-directed maintenance approach rather than as a quantitative dose translation of monotherapy RCT outcomes. Product-specific clinical validation, lifestyle co-administration (hydration, post-coital voiding, avoidance of unnecessary antibiotic courses), and ongoing regulatory-adjudication monitoring are central to responsible commercialisation.

24. Declarations

Author contributions. Authors conceptualised the review, designed the search strategy, drafted the manuscript, performed mechanistic interpretation, critical revision, and approved the final version. All authors have read and approved the submitted manuscript and agree to be accountable for its content.

Conflicts of interest. *Choose one:*

All the Authors are employees of Biotex Life Solutions. Authors declare no competing financial interests. The funder had no role in literature search, data interpretation, or the decision to submit.

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Data availability. No new datasets were generated or analysed in support of this review. All sources cited are publicly available; DOIs are listed in the reference list. No patient-level data, animal data, or unpublished proprietary data were used.

Ethics approval and consent to participate. Not applicable. This article is a narrative review of previously published literature and did not involve human participants, animals, patient records, or identifiable personal data. No institutional review board approval was required.

Consent for publication. Not applicable (no individual participant data, images, or identifiable information are reported).

Use of AI-assisted tools. "AI-assisted tools were used under direct author supervision for grammar refinement, reference-formatting consistency, and cross-checking of numerical values against source text. All scientific claims, mechanistic interpretations, and final manuscript content are the authors' own."

Systematic-review registration. Not applicable. This is a narrative review, not a registered systematic review or meta-analysis.

25.Abbreviations

ADME, absorption, distribution, metabolism and excretion; AUA, American Urological Association; BL-DMAC, Brunswick Laboratories 4-(dimethylamino)cinnamaldehyde assay; BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; CUA, Canadian Urological Association; CVD, cardiovascular disease; DBP, diastolic blood pressure; DOI, digital object identifier; EFSA, European Food Safety Authority; FDA, United States Food and Drug Administration; FimH, type-1 fimbrial adhesin H; FMD, flow-mediated dilation; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HDL, high-density lipoprotein; HPLC, high-performance liquid chromatography; IBC, intracellular bacterial community; ICH, International Council for Harmonisation; INR, international normalised ratio; JAMA, Journal of the American Medical Association; LDL, low-density lipoprotein; MDA, malondialdehyde; NCCIH, National Center for Complementary and Integrative Health; NDA, EFSA Panel on Nutrition, Novel Foods and Food Allergens; NHS, National Health Service; NIHR, National Institute for Health and Care Research; NSAID, non-steroidal anti-inflammatory drug; ORCID, Open Researcher and Contributor Identifier; PAC, proanthocyanidin; PapG, P-fimbrial adhesin G; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QIR, quiescent intracellular reservoir; RCT, randomised controlled trial; RR, relative risk; rUTI, recurrent urinary tract infection; SBP, systolic blood pressure; SMX, sulfamethoxazole; SOD, superoxide dismutase; SUFU, Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction; TAC, total antioxidant capacity; TMP, trimethoprim; UPEC, uropathogenic *Escherichia coli*; USP, United States Pharmacopeia; UTI, urinary tract infection.

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