Systematic review of the effect of D-mannose with or without other drugs in the treatment of symptoms of urinary tract infections/cystitis (Review)

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Abstract. Several studies, reviews and meta-analyses have documented that D-mannose use lowers the risk of recurrent urinary tract infections (UTI), but its role in the treatment of UTI/cystitis-related symptoms is unclear. In particular, no systematic review has analyzed the role of treatment with D-mannose in acute UTI/cystitis. In this paper, we systematically reviewed the published data on the effect of D-mannose, alone or in association with other compounds, on the typical symptoms of UTI/cystitis. PubMed/Medline and EMBASE databases were searched, from 1990 to January 2022, using combinations of the following keywords: 'urinary tract infections', 'cystalgia', 'recurrent next urinary tract infection', 'cystitis', 'mannose', 'mannoside', 'D-mannose', 'bacteriuria', 'pyuria', 'pyelocystitis' with the appropriate Boolean modifiers (Limits: Human, English, full article). Studies were selected for the systematic review if they were clinical studies and reported original data, the number of patients using D-mannose alone or in association with other treatments, and the number of patients with symptoms of UTI/cystitis at trial entry and after the follow-up period. A total of seven studies were identified. D-mannose was given alone in two studies, and was associated with cranberry extract, *Morinda citrifolia* fruit extract, pomegranate extract, fructo-oligosaccharides, lactobacilli, and N-acetylcysteine in the others. All studies reported that symptoms decreased after treatment with D-mannose. Despite the limitations of the studies, the consistent results observed among all studies give support to the general findings that D-mannose may be useful in the treatment of UTI/cystitis symptoms.

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1. Introduction

Urinary tract infections (UTI) are a common condition. Among them, cystitis is the most frequent disease. Treatment for UTI/cystitis ranges from over-the-counter medications to antibiotics if the cause is an infection. In such patients, antimicrobials are often inappropriately prescribed, and their use is associated with the selection of antimicrobial-resistant organisms colonizing or infecting the urinary tract (1).

The rise in antimicrobial resistant organisms is becoming a relevant clinical and public health issue. Worldwide, it has been estimated that ~10,000,000 deaths by 2050 will be attributable to antibiotic resistance (2).

Recent guidelines from the main international associations, such as the American and Canadian Urological Associations, and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (3), and the recent scientific literature (4,5) have underlined the importance of limited antibiotic use and of new research on molecules that interact with bacterial load or virulence mechanisms of uropathogens for the treatment of UTI.

Among these molecules, several studies have identified D-mannose (6-12), which is characterized by a non-pharmacological, non-metabolic, non-bacteriostatic or bactericidal, but biomechanical mechanism of action and does not affect antibiotic resistance (13).

2. Mechanism of action of D-mannose in the prevention and treatment of UTI

D-mannose is a monosaccharide naturally produced by the body from glucose. It is present in the body cells and in some foods. D-mannose differs from glucose by inversion of one of the four chiral centers of the molecule, precisely that on the

carbon atom in the position 2. D-mannose is the 'C-2 epimer' of glucose (14,15).

At least 90% of ingested D-mannose is absorbed in the upper part of the intestine. Its peculiarity is that despite it being a simple molecule, this sugar is not metabolized by the organism. Consequently, it is not stored in the liver or other organs, but it is excreted unconverted into the urine via the kidneys. About 60 min after ingestion, it arrives unchanged in the urinary tract. D-mannose also has no effect on human metabolism after long-term use (16,17).

The most common agent of cystitis is the uropathogenic *E. coli* (UPEC). UPEC adheres to urothelial cells mainly through the interaction between FimH (a fimbrial adhesin) and mannosylated uroplakin proteins, which are the main determinants of the urovirulence of UPEC (2).

Several studies have shown that, in the urine, *E. Coli* attaches to D-mannose. This mechanism is based on the structural similarity between D-mannose and urothelial mannosylated receptors exposed by the epithelium of the urinary tract. Consequently, D-mannose prevents FimH-mediated bacterial adhesion to the bladder wall through a competitive inhibition mechanism (18).

Since the process of bacterial adhesion on the urothelial cell's surface is a determinant of the start of UTI, D-mannose was shown to be effective in treating UTIs caused by *E. Coli* (7,10). D-mannose exerts a urothelial barrier function, inhibiting the adhesion of bacteria to the urothelium. Binding free D-mannose, bacteria are blocked in the urine and then eliminated by the urinary tract (19). As a consequence of this mechanism, *in vivo* and *in vitro* studies have demonstrated that mannose-like molecules lower bacterial load 2-4 fold in the urinary tract and in the bladder (20).

This effect is also present in the case of concurrent antibiotic therapy. In fact, D-mannose has no bacteriostatic and/or bactericidal activity and does not modify the bacterial cell, thus it does not interfere with the action of antibiotics (2,21).

Furthermore, it has been suggested that the dosages of D-mannose used in clinical practice does not affect E. coli metabolism and growth and does not modify bacterial adhesiveness causing FimH variants. All these characteristics underline the fact that the long term use of D-mannose is safe (18).

Several studies, reviews and meta-analyses have shown that D-mannose use lowers the risk of recurrent (r)UTI (22,23). Less data has been published regarding the role of D-mannose in the treatment of UTI/cystitis related symptoms. In particular, to the best of our knowledge, no reviews have been published on the role of D-mannose in the treatment of acute UTI/cystitis, i.e., on the use of d-mannose not as prevention of recurrence but as treatment of acute symptoms.

In this paper, we have performed a systematic review of the available data on the effect of D-mannose on the typical symptoms of UTI/cystitis given alone or in association with other compounds.

3. Literature search methodology

Literature search. We searched PubMed (National Library of Medicine, Washington, DC) and EMBASE databases from 1990 to January 2022 using combinations of the key words: 'mannose', 'mannoside', 'D-mannose', 'bacteriuria', 'pyuria', 'pyelocystitis', 'cystitis', 'urinary tract infections', 'cystalgia, recurrent next urinary tract infection' with the appropriate Boolean modifiers (limits: full article, human, English). After the original search, we reviewed the reference lists of the identified articles to identify other pertinent studies.

Two authors reviewed the papers and independently identified the eligible articles for the systematic review and extracted the data. Any disagreement was solved after discussion with a third reviewer.

Studies were considered if they met all the following criteria: Clinical studies, studies reporting original data, studies reporting the number of patients using D-mannose alone or in association with other treatments, studies reporting number of patients with symptoms of UTI/cystitis at trial entry and after the follow-up period. Reviews, commentaries, and case reports were excluded.

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (24,25) and registered in the PROSPERO database (registration no. CRD42022303244).

Data extraction. A PICOS (Patient, Intervention, Comparator, Outcome, Study) structure was used for defining the study questions and the inclusion/exclusion criteria. The question was: 'Is D-mannose effective in the treatment of symptoms of UTI/cystitis?' (Table I).

For each study, the following information was extracted: First author's last name; year of publication; country of origin; design of the study; number of subjects treated with D-mannose; age if present; criteria for study entry; type or severity of symptoms at study entry and at follow up visit; type and dose of drug; and length of follow-up.

To evaluate the effect of D-mannose on the symptoms of UTI /cystitis, from the studies that presented data on long-term follow-up, we only considered information obtained during the evaluation of first symptoms after study entry.

Quality assessment. The quality of the studies included in the review was evaluated using the Newcastle-Ottawa scale (NOS) (26). Studies were evaluated according to three broad categories: Selection of study groups, comparability of study groups, and assessment of outcome (cohort studies) or ascertainment of exposure (case-control studies). The maximum score was 9.

For Randomized Controlled Trials (RCTs), the Revised Cochrane risk-of-bias tool for randomized trials was used (27).

4. Systematic review

Our search retrieved 477 abstracts from PubMed/MEDLINE, and 201 from Embase (Fig. 1). After reviewing the abstracts, a total of 21 publications were identified that were fully read. Two studies were excluded as the full text was not in English (28,29), 11 studies (19,30-39) were excluded as they did not report the data on symptoms of UTI/cystitis, but only the risk of recurrent UTI or the frequency of UTI in patients submitted to urodynamics, and one (40) study was excluded as it reported a Visual Analogic Scale (VAS) evaluation of symptoms 12 months after study entry, but included women

Table I. PICOS criteria for inclusion and exclusion of studies.

Parameter	Inclusion criteria	Data extraction
Patient	Women with symptoms of low urinary tract infection/cystitis	Location, age, type of patients
Intervention	D-mannose	Dose and duration
Comparator	No treatment	Group definition
Outcome	Reduction of symptoms	Number of cases, type of assessment
Study	Cross-sectional, cohort, case–control studies, clinical trials	Type of study design

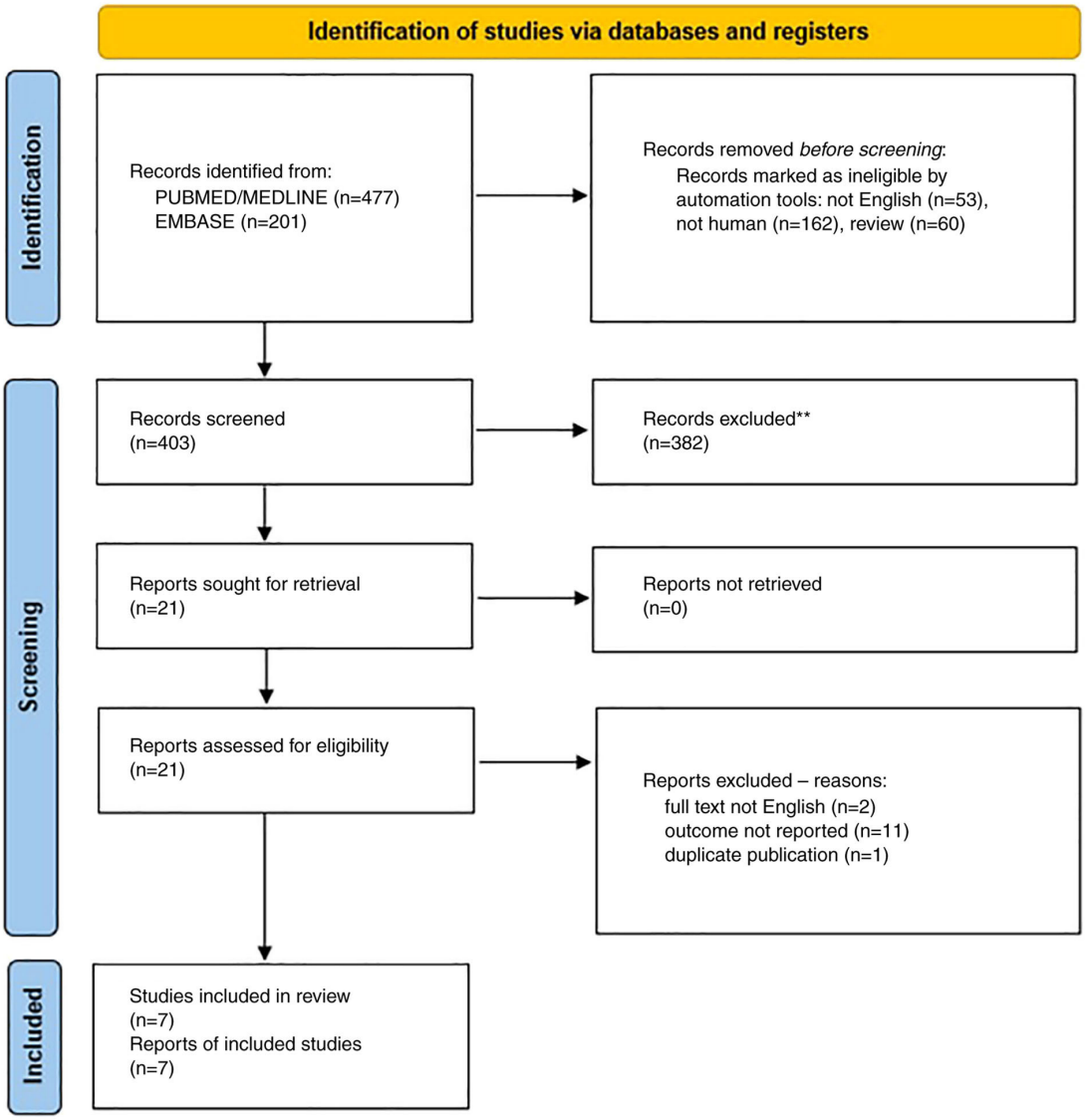

Figure 1. Flow chart of literature search.

with rUTI without any specific indication of symptoms of UTI/cystitis at study entry.

A total of 7 studies were identified (6-12). Their primary methodological characteristics are presented in Table II. A total of four studies were prospective uncontrolled studies (7,8,10,11), one was a retrospective chart review case-controlled study (9) and two were randomized controlled trials (6,12). All but one of the studies (10), included only women. The sample size ranged from 33-93 subjects.

With regard to the study drug, D-mannose was given alone in only two studies (6,8). In the study by Del Popolo and Nelli (10), D-mannose was given alongside dry willow extract (salicin) in the first phase of the study and with Lactobacillus acidophilus in the second phase. In the other studies D-mannose was given alongside several other compounds, including cranberry extract, *Morinda citrifolia* fruit extract, pomegranate extract, fructo-oligosaccharides, lactobacilli, and N-acetylcysteine.

Table II. Main characteristics of selected studies.

First author, year	Study design	Country	Cohort	Inclusion criteria	Sample size, n	Drug doses	Control group	Follow-up	Mode of symptoms quantification	(Refs.)
Porru *et al*, 2014	Randomized cross over trial	Italy	Women aged ≥18 years (range 22-54)	Acute symptomatic cystitis and history of rUTI	46	Oral D-mannose 1 g three times a day, for 2 weeks, and subsequently 1 g twice a day for 22 weeks	5-day antibiotic therapy with TMP/SMX 160 mg/800 mg twice a day, followed by a single dose at bedtime for 1 week each month in the following 23 weeks	24 weeks	VAS	(6)
Vicariotto, 2014	Prospective uncontrolled	Italy	Premenopausal women aged >18 years	Acute uncomplicated cystitis diagnosed by urine dipstick testing and an evaluation of the presence of typical symptoms	33	250 mg D-mannose/ 500 mg of a high PACs cranberry extract/2.5 billion live cells *L. plantarum LP01*/1 billion viable cells, *L. paracasei LPC09*/1 billion viable cells *S. thermophilus ST10*, 250 mg tara gum. 2 doses/day for 1 month, then 1 sachet/day for 1 month.	-	30 weeks	UTI-Symptoms Assessment Questionnaire	(7)
Domenici *et al*, 2016	Prospective uncontrolled	Italy	Women aged 18-65 years	Acute cystitis and/or history of rUTIs	43	D-mannose (1.5 g), sodium bicarbonate, sorbitol and silicon dioxide twice daily for 3 days and then once a day for 10 days.	-	15 weeks	UTI-Symptoms Assessment Questionnaire	(8)

Table II. Continued.

First author, year	Study design	Country	Cohort	Inclusion criteria	Sample size, n	Drug doses	Control group	Follow-up	Mode of symptoms quantification	(Refs.)
Marchiori and Zanello, 2017	Retrospective case control study	Italy	Women with a diagnosis of breast cancer treated with aromatase inhibitors or tamoxifen or LHRH analogs	Women with rUTI complaining urogenital discomfort	60 (Group 1 40 Group 2: 20)	D-mannose 500 mg, N-acetylcysteine 100 mg and Morinda citrifolia fruit extract 200 mg (NDM) 1 vial every 12 h for 60 days and then 1 vial every 24 h for 4 months, associated with antibiotic therapy (see Group 2)	Antibiotic therapy, depending on microbial sensitivity (Fosfomycin, 3 g per day for 2 days or nitrofurantoin 1 cprs 100 mg three times a day for 6 days or ciprofloxacin 1,000 RM or prulifloxacin 600 mg 1 cps/day for 6 days)	2 months	Verbal rating scale ranking form 0 (absence of symptoms) to 4 (severe symptom)	(9)
Del Popolo and Nelli, 2018	Prospective uncontrolled	Italy	Men and women attending a neuro-urologic clinic	Symptomatic UTI and history of rUTI	78 patients (17 men) 39 patients had neurogenic bladder	5-days regimen with a tid oral combination of 1,000 mg of D-mannose plus 200 mg of dry willow extract (salicin) followed by bid 7-days with 700 mg of D-mannose plus 50 mg (1x109 CFU) of Lactobacillus acidophilus (La-14).	-	2 weeks[a]	VAS	(10)
Pugliese *et al*, 2020	Prospective uncontrolled	Italy	Women (mean ± SD Age 38±11.2)	Women with urinary symptoms suggestive of UTI	33	D-mannose 2 g/fructo-oligosaccharide 1 g/pomegranate extract 250 mg (with 70% titration of ellagic acid 175 mg)/Lactobacillus plantarum (Lp115 ≥ 2 billion colony-forming unit) 2 times daily for 5 days and then once a day for 10 days	-	15 days	Acute Cystitis Symptoms Score	(11)

Table II. Continued.

First author, year	Study design	Country	Cohort	Inclusion criteria	Sample size, n	Drug doses	Control group	Follow-up	Mode of symptoms quantification	(Refs.)
Rădulescu *et al*, 2020	Randomized control trial	Romania	Non-pregnant, healthy women aged 18-60 years (mean ± SD age 39.77±10.36 years)	Uncomplicated lower urinary tract infection	93	D-mannose 1 gr/400 mg cranberry extract for 7 days plus TMP-SMX	TMP-SMX alone for 7 days.	7 days	7 items questionnaire (dysuria, increased urinary frequency/ pollakiuria, urinary urgency, hematuria, hypogastric pain, lumbar pain, vesical tenesmus) and 3 degrees of intensity (absent, moderate, severe).	(12)

[a]The results at 12 weeks were not considered. LHRH, Luteinizing Hormone Releasing Hormone; PACs, proanthocyanidins; SMX, sulfamethoxazole; TID, twice daily; TMP, trimethoprim; UTI, urinary tract infection; rUTI, recurrent UTI; VAS, visual analogue scale.

Four studies evaluated the changes in symptoms in the short term (7-15 days) (8,10-12), one after 30 days (7), one after 60 days (9) and one after 24 weeks (6).

Quality of selected studies. Considering the observational studies using the NOS tool, study quality was constantly 5/9. There was the possibility that some evaluation using the NOS quality items was debatable (i.e., if the sample size was too little to control for important factors or if a not exposed cohort did exist). The two trials (6,12) had a low risk of bias according to the Cochrane risk of bias tool (Table III).

To facilitate the reading of the systematic review, we summarized the main results of the selected studies in Table IV.

Porru *et al* (6) conducted a randomized cross-over trial including women with an acute symptomatic UTI and three or more rUTIs during the 12 months before study entry. A total of 60 women were randomly divided into an antibiotic treatment with trimethoprim/sulfamethoxazole or oral D-mannose three times a day group, for 2 weeks (phase of the study considered in this review). The primary endpoint, which was out of the scope of this review, was the evaluation of the elapsed time to recurrence. We included the secondary endpoints, which were bladder pain (VASp) and urinary urgency (VASu). Mean VASp score, mean VASu score, and average number of 24-h voiding events decreased significantly after 2 weeks of treatment. Methods for taking into account the period effect were not clearly stated. The authors did not report any adverse events.

Vicariotto (7) reported the results of a small prospective observational study. Eligible for the study were 33 premenopausal, nonpregnant women diagnosed with acute uncomplicated cystitis. Patients were given a compound including D-mannose, cranberry dry extract, exopolysaccharides produced by Streptococcus thermophilus ST10, tara gum, *Lactobacillus plantarum*, and *Lactobacillus paracasei*, two doses per day for 1 month. At baseline and in the 30 day visits the following symptoms were evaluated: Dysuria, frequent voiding, urgency, and suprapubic pain. A statistically significant improvement was observed.

Domenici *et al* (8) reported an observational prospective study. A total of 43 women with acute cystitis were included. D-mannose was administered twice daily for 3 days and then once a day for 10 days. Patients' symptoms, the therapeutic effects and quality of life (QoL) were evaluated clinically using a validated questionnaire (UTISA) (41) The mean UTISA scores significantly improved for most symptoms between baseline and follow up visits.

Marchiori and Zanello (9) studied the effectiveness of D-mannose in association with N-acetylcysteine and *Morinda citrifolia* fruit extract (DNM) plus antibiotic therapy, in recurrent cystitis. A total of 60 women with breast cancer and recurrent cystitis were analyzed retrospectively. Of these, 40 patients received antibiotic therapy plus DNM and 20 women antibiotics alone for 6 months. After 2 months of study entry, women treated with DNM plus antibiotic therapy exhibited a more prominent improvement in urgency, frequency, urge, incontinence, bladder and urethral pain in comparison to women treated with antibiotics alone.

Del Popolo and Nelli (10) reported an observational uncontrolled prospective study including 85 patients (68 women and 17 men) with symptomatic UTI and a history of rUTI.

Table III. Evaluation of the study quality according to the Newcastle-Ottawa Scale (cohort studies) or Cochrane risk of bias (randomized clinical trials).

Cohort study[a]	Question #	Selection	Question #	Comparability	Question #	Outcome (Cohort studies)	Study quality	(Refs.)
Vicariotto, 2014	1	*	1	-	1	-	5/9	(7)
	2	-	2	-	2	*		
	3	*			3	*		
	4	*						
Domenici *et al*, 2016	1	*	1	-	1	-	5/9	(8)
	2	-	2	-	2	*		
	3	*			3	*		
	4	*						
Marchiori and Zanello, 2017	1	*			1	-	5/9	(9)
	2	-	1	-	2	*		
	3	*	2	-	3	*		
	4	*						
Del Popolo and Nelli, 2018	1	*			1	-	5/9	(10)
	2	-	1	-	2	*		
	3	*	2	-	3	*		
	4	*						
Pugliese *et al*, 2020	1	*	1		1	-	5/9	(11)
	2	-	2	-	2	*		
	3	*		-	3	*		
	4	*						
Randomized clinical trials[b]							Overall risk of bias	
Porru *et al*, 2014	Randomization: low risk						Low	(6)
	Assignment to intervention: low risk							
	Adhering to intervention: low risk							
	Missing outcome: low risk							
	Measure of outcome: low risk							
	Selection of results: low risk							
Rădulescu *et al*, 2020	Randomization: some concerns						Low	(12)
	Assignment to intervention: some concerns							
	Adhering to intervention: low risk							
	Missing outcome: low risk							
	Measure of outcome: low risk							
	Selection of results: low risk							

[a]The Newcastle-Ottawa quality assessment scale was used for cohort studies, and the maximum score was 9. Most items were evaluated as '-' due to the small sample size or lack of information on the cohort. [b]For the assessment of randomized controlled studies, the revised Cochrane risk of bias tool was used.

A total of 78 patients received a 5-day regimen consisting of thrice daily oral D-mannose and dry willow extract (salicin), followed by a 7-day regimen of twice daily D-mannose and *Lactobacillus acidophilus*. Patients' symptoms were evaluated using a 3-day bladder diary and a VAS, 15 days after study entry. VAS scores decreased from 8.07±1.70 to 4.74±2.07 (P=0.001) in non-neurological patients (39 subjects, group A) and from 7.21±1.90 to 3.74±3.12 (P=0.001) in the neurological patients (39 subjects, group B). A significant reduction in daily frequency was noted in both groups, from 14±3 to 7±3 (P=0.001) in group A and from 15±3 to 8±3 (P=0.001) in group B.

D-mannose, pomegranate extract, prebiotics and probiotics were given twice daily for 5 days and then once a day for 10 days to 33 women (mean age 38.1±11.2 years) with urinary symptoms suggestive of an UTI, in a study conducted by Pugliese *et al* (11). Antibiotics were permitted on a clinical basis. Changes in patients' symptoms were evaluated using the Acute Cystitis Symptom Score (42,43) at baseline (T0), and 15 (T1) and 30 (T2) days later. For the purpose of this review, the

Table IV. Results of selected studies[k].

Study, year	Methods for evaluation of the symptoms	Suprapubic pain	Dysuria	Frequent voiding	Urgency	Hematuria	Overall symptoms evaluation	(Refs.)
Porru *et al*, 2014	VAS							(6)
Before D-mannose		4.1 (1.1)[c]		7.1 (1.1)[b]	4.6 (1.1)			
After D-mannose		2.2 (0.5)[a]		4.7 (1.0)[a]	2.6 (0.7)[a]			
Vicariotto, 2014	UTI-SAQ							(7)
Baseline		1.39	2.03	2.18	2.15	0.61		
Day 30		0.97[a]	1.36[a]	1.70[a]	1.64[a]	0.58		
Domenici *et al*[b,h], 2016	UTI-SAQ							(8)
Baseline		1.47 (0.95)	1.60 (±1.00)	2.16 (1.52)	1.73 (0.92)	0.34 (0.90)		
Day 15		0.15 (0.36)[a]	0.31 (0.47)[a]	0.60 (0.63)[a]	0.23 (0.43)[a]	0.10 (0.45)		
Marchiori and Zanello, 2017	VRS							(9)
Cases								
Baseline		32.5% (13/40)[e,j]		62.5% (25/40)	37.5% (15/40)[f]			
2 months		25% (10/40)		5% (2/40)	0% (0/40)			
Control group								
Baseline		50% (10/20)		35% (7/20)	20% (4/20)			
2 months		45% (9/20)		25% (5/20)	5% (1/20)			
Del Popolo and Nelli, 2020	VAS							(10)
Neurogenic bladder group								
Baseline				14.0 (2.6)[d]			8.07 (1.70)[h]	
2 weeks				6.9 (1.3)[a]			4.74 (2.07)[a]	
Non neurogenic bladder group								
Baseline				15 (3)[b]			7.21 (1.9)	
2 weeks				8 (3)[a]			3.74 (3.12)[a]	
Pugliese *et al*, 2020	ACSS							(11)
Baseline							11.5[i] (95% CI, 10.5-12.6)	
15 days							4.9[a] (95% CI 4.0-5.9)	
Rădulescu *et al*[l], 2020	3 degrees							(12)
Cases	questionnaire							
Baseline		72.9 (35/48)[g,j]	60.4 (29/48)	85.4 (41/48)	89.6% (43/48)	10.4% (5/48)		
7 days		2.1 (1/48)	0% (0/48)	2.1% (1/48)	0% (0/48)	0% (0/48)		

Table IV. Continued.

Study, year	Methods for evaluation of the symptoms	Suprapubic pain	Dysuria	Frequent voiding	Urgency	Hematuria	Overall symptoms evaluation	(Refs.)
Control group								
Baseline		86.7% (39/45)	55.6% (25/45)	82.2% (37/45)	80% (36/45)	22.2% (10/45)		
7 days		2.2% (1/45)	6.7% (3/45)	8.9% (4/45)	4.4% (2/45)	0% (0/45)		

[a]P<0.05. [b]Domenici *et al* also reported a statistically significant reduction of back pain and nycturia. [c]Pain not otherwise specified. [d]Number of voiding events/24 h. [e]Bladder and urethral pain. [f]Imperious urination. [g]Vesical tenesmus. [h]Evaluation of all symptoms. [i]Typical symptoms score. [j]Moderate or severe/total subjects. [k]Unless otherwise specified, data are presented as mean and standard deviation. [l]Rădulescu *et al* also reported a decrease of lumbar pain and hypogastric pain. UTI-SAQ, UTI-Symptoms Assessment Questionnaire; VRS, verbal rating scale; ACSS, Acute Cystitis Symptoms Score; CI, confidence interval; VAS, visual analogue scale.

results at T1 were considered. At T1, all or most of the symptoms disappeared in 10 women (30.3%), whereas they persisted or worsened in 7 patients (21.2%). Mean scores for typical symptoms (i.e. frequency, urgency, pain or burning with urination, pain in the suprapubic area, feeling of incomplete bladder emptying, and gross hematuria) decreased significantly from 11.5 [95% confidence interval (CI) 10.5-12.6)] to 4.9 (95% CI 4.0-5.9) (P<0.0001). For differential symptoms (i.e., lower back pain, vaginal discharge, urethral discharge, fever, and chills), mean scores decreased from 3.1 (95% CI 2.6-3.6) to 0.6 (95% CI 0.3-0.9) (P<0.0001). The QoL mean score also decreased from 7.2 (95% CI 6.7-7.7) to 4.0 (95% CI 3.3-4.6) (P<0.0001). Antibiotics were given to six patients. No adverse events were reported.

Rădulescu *et al* (12) reported a randomized study including 93 non-pregnant healthy women (mean age of 39.77±10.36 years) diagnosed with uncomplicated lower UTI. Patients were given antibiotics alone or in association with D-mannose plus cranberry extract for 7 days. Co-administration of D-mannose plus cranberry extract was not associated to statistically significant differences in symptoms, except for urinary urgency/pollakiuria (P=0.024).

5. Discussion

This systematic review is, to the best of our knowledge, the first attempt to systematically review the published data on the effect of D-mannose in the treatment of acute symptoms of UTI/cystitis. The results of this evaluation suggest that, in women with symptoms of UTI/cystitis, treatment with D-mannose alone or in association with other compounds is useful for lowering the intensity of symptoms both in the short and middle-term for all typical symptoms, except hematuria.

However, this finding has several limitations and should be considered cautiously. First, the limited data do not provide the opportunity for analysis in detail of the role of different doses of D-mannose or the effect of D-mannose alone or in association with other compounds. Furthermore, most data were derived from uncontrolled studies. In general, the findings from this analysis are based on an extremely limited number of studies with small sample sizes.

The populations included in the considered studies are markedly heterogeneous. For example, the study conducted by Del Popolo and Nelli (10) included men and women with neurological problems. Otherwise, the majority of studies included only women in the premenopausal period (6,7,11). Furthermore, as the methods of evaluation of symptoms differed, any comparison among studies of the magnitude of the effect of D-mannose is not feasible. Moreover, we also must take into account that the majority of included studies were conducted in Italy. That is, it is conceivable that only studies showing positive results were published in an international journal, whereas negative findings were instead published in local journals (44). Finally, limiting our analysis to publications in English language journals may have reduced the completeness of information, causing bias.

A strength of this analysis is that previous reviews and meta-analyses considered the role of D-mannose in the prevention of UTI recurrence (22,23), whereas we summarized the

available evidence regarding its use in the treatment of UTI symptoms. However, from a biological point of view, our findings have a rationale, since D-mannose binds to the tip of type 1 pili and saturates adhesin FimH, blocking bacterial adhesion to the urothelium and the consequent urothelial invasion (45).

All these considerations were suggested to explain the well-documented role of D-mannose in lowering the risk of recurrent infections in women with rUTI. Less clear is the potential mechanism of D-mannose on UTI/cystitis symptoms. However, the fact that D-mannose interacts with bacteria to promote UPEC excretion may explain a faster resolution of symptoms (18).

We were not able to analyze the effect of D-mannose on different uropathogenetic agents separately. However, although type 1 fimbriae were extensively studied in E. coli, type 1 pili were documented in several other uropathogens commonly involved in rUTIs (23). Furthermore, recently, Zhang *et al* (46) suggested that D-mannose could play a role as an immune modulator. It was shown that prolonged exposure to D-mannose did not select FimH variants that modify bacterial adhesiveness after D-mannose removal, further indicating that it does not exert 'antibiotic-like' activity (21). Along this line, we have observed similar effects in short and middle-term treatments.

In conclusion, despite the limitations, consistent results among all studies give strong support to the general findings. Although the biological and clinical explanations of our results are not entirely clear, observational studies and clinical trials consistently suggest that D-mannose may be useful in the treatment of UTI/cystitis symptoms. Its non-pharmacological, non-metabolic, non-bacteriostatic or bactericidal, but biomechanical mechanism of action, and the fact that it does not affect antibiotic resistance may support the use of D-mannose in the treatment of UTI/cystitis.

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Availability of data and materials

All data generated or analyzed during this study are included in the published article.

Authors' contributions

FP and FF designed the study. FC, SC and GE searched the literature, selected the papers and extracted the data. SC and ER confirm the authenticity of all the raw data. FP and ER wrote the paper. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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