

D-mannose Use for Bacterial Urinary Tract Infections in Dogs and Cats

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Abbreviations

E coli

FimH

UTI

Escherichia coli

Gene for type 1 fimbrin

D-mannose specific adhesin

Urinary tract infection

Abstract

D-mannose is a 6-carbon sugar that has benefits in complementary therapy in veterinary medicine. The most researched application is in the treatment and prevention of urinary tract infections (UTIs) caused by *Escherichia coli* (*E coli*). Research has shown that *E coli* has mannose receptors on its fimbriae which bind to D-mannose, preventing it from attaching to the uroepithelium. As a result, the bacteria are eliminated during urination instead of colonizing urinary tissues. Since recurrent UTIs are common in dogs and cats, in cases in which the infection is due to outside factors, preventive use of D-mannose can be of value. Benefits include low cost, low incidence of adverse effects, and perhaps less risk for development of antibiotic resistance. D-mannose should be considered as a standard preventive measure when formulating treatment plans for patients with recurrent UTIs.

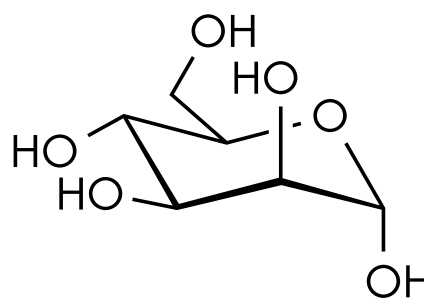
Introduction

Signs of a urinary tract infection (UTI) in dogs are a common veterinary presentation. It is estimated that about 10% of patients have this complaint (1). Single episodes of UTI generally resolve quickly with antibiotic therapy, but recurrent infections occur in some dogs and cats due to a number of predisposing factors. It is with these presentations that D-mannose may have its greatest impact. When D-mannose binds to susceptible *Escherichia coli* (*E coli*) bacteria, it prevents colonization of the uroepithelium that could perpetuate the infection. The D-mannose–bacteria combination is then eliminated from the bladder via urination. Another key benefit to the use of D-mannose is that it may reduce the need for multiple antibiotic treatments, thus decreasing the expansion of microbial resistance.

Structure and Sources of D-mannose

D-mannose is a 6-carbon simple sugar that is an isomer of dextrose (Figure 1). Other names for this compound include carubinose, D-manosa, mannose, and seminose (2, 3). This sweet-tasting compound is found to occur naturally in some plants such as Chinese jujube (*Zizyphus jujube*), apple flesh, mango, and cranberry larch (3, 4). It is also found in oranges, peaches, blueberries, and cranberries. D-mannose may be produced commercially via extraction from various plants as well as by microbial fermentation (3).

Figure 1



D-mannose

Chemical structure of D-mannose

Pharmacokinetics

D-mannose is readily absorbed following oral administration. In humans, approximately 90% of ingested D-mannose is taken up in the small intestine and then quickly excreted by the kidneys (5). Within 30 to 60 minutes,

large amounts of the compound are removed from the circulatory system unchanged, resulting in a rapid increase in the concentration of D-mannose in the urine (5).

D-mannose that is not excreted can be made available for cellular utilization via uptake by hexose transporters on the cell membranes (6). In the body, D-mannose is involved in protein glycosylation which is essential to ensure that proteins are properly configured for their eventual use. Sugars such as D-mannose often function as ligands for receptors to mediate cell attachments and communication pathways (7).

Mechanism of Action

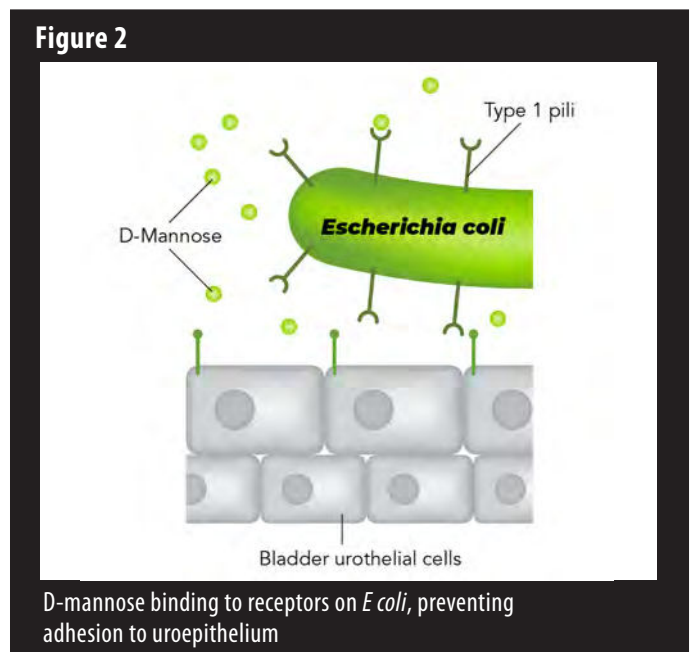
There are several proposed mechanisms of action for D-mannose, depending upon its intended function. It has been most studied for the prevention and treatment of bacterial UTIs.

Since D-mannose is not metabolized like other sugars, the majority is filtered by the kidneys and remains in the bladder until excreted, where it can bind with any pathogenic bacteria present in the urinary tract. Gram-negative rods in the Enterobacteriaceae family contain fimbriae that can bind to both D-mannose and urinary epithelium via type 1 fimbriae. D-mannose specific adhesin (FimH), a molecule composed of a pilin and a mannose-binding lectin (6, 8). It is thought that D-mannose can form up to 12 hydrogen bonds with the FimH adhesins on the bacteria, thus preventing it from attaching to the urinary epithelium (5). *E. coli*'s glycoprotein lectin adheres to the first appropriate contact it encounters, so if that encounter is D-mannose, those bacteria can no longer bind to urinary tissues (Figure 2). Glycoprotein receptors present on the bladder wall are similar in structure to D-mannose; when the bacteria encounter and bind with D-mannose, they are unavailable to colonize the bladder tissue. If there is a sufficient concentration of D-mannose in the urine, colonization will be minimized. In an animal trial, concentrations as low as 20 µg/ml blocked adherence to the urinary epithelium (9). This may reduce the risk of UTIs with mannose-sensitive bacteria, as the mannose-bacteria complexes are cleared during urination (5). Because the compound itself is eliminated with each urination, ongoing administration of D-mannose is required to achieve this effect (10).

D-mannose does not kill bacteria or modify their pathogenicity. The binding is a physical interaction with no opportunity for bacterial transformation; therefore, there is no concern for the creation of resistance to the compound (5). Additionally, D-mannose does not impact bacterial viability or metabolism or interfere with concurrently administered antibiotics (11).

Bacterial adhesion to tissue is not always a simple process. Bacteria with mannose receptors are most often responsible for the colonization of urinary tissue; however, not all species of bacteria bear the mannose-binding capacity (12). Although not available as a commercial test, mannose receptivity can be determined in vitro by hemagglutination (13). If the bacterial species present is mannose resistant, there will be no benefit to administering D-mannose to a patient. If there is no improvement in clinical signs within 24 hours, alternative treatments must be pursued. D-mannose will also be ineffective if the pathogenic bacteria are protected in a biofilm on the bladder mucosa (12). Biofilms consist of the bacteria themselves plus a mucopolysaccharide matrix used for protection from antibiotics and from the host's immune system (12). *E. coli* can create biofilms either within cells or on the surface. These biofilms protect the bacteria and can result in a quiescent population capable of resurgence. Biofilm formation may begin within 24 hours of infection and may result in either persistent or recurrent UTI (12, 14).

The body does mount defenses against bacterial colonization in the form of secretory IgA and glycosaminoglycans lining the bladder wall, as well as the flushing action produced by frequent urination (15). Additionally, the uroepithelium contains proteins such as Tamms-Horsfall protein that help prevent bacterial attachment. D-mannose mimics the binding function of these proteins (4).



Clinical Signs and Predisposing Factors of Recurrent Urinary Tract Infections

Veterinarians are familiar with the signs of UTI such as dysuria, pollakiuria, and urinary urgency, but confirmation

of bacterial infection via urinalysis is necessary for diagnosis. Recurrent UTI is defined as 3 or more episodes per year (16). Collection of urine via cystocentesis for culture and sensitivity is essential in order to identify appropriate antibiotic therapy. About 14% of dogs will experience a bacterial UTI throughout their lives (17). This number is much smaller for cats, only 1 to 3%, usually in aged patients. Additionally, feline bacterial cystitis may be more difficult to confirm. In 1 study with 155 cats with confirmed bacteriuria, 35% showed no clinical signs (15). This makes gathering a minimum database even more important for cats.

The median age for dogs with recurrent UTIs is 7 years. Females appear to be at increased risk in both dogs and cats (18, 19).

A number of factors may predispose a patient to develop recurrent UTIs. In the young, these may be congenital abnormalities or malformations. In adult dogs and cats, predisposing factors include having a recessed vulva, neurologic issues such as urinary retention or inability to fully empty the bladder, or a history of urinary catheterization or surgery, especially urethrostomy. Administration of immunosuppressive drugs, including corticosteroids, is an important predisposing factor. In older animals, systemic diseases such as chronic kidney disease, hyperadrenocorticism, diabetes mellitus, and hyperthyroidism can all predispose patients to UTIs (20).

Another factor is the formation of biofilms by *E coli*. Once established on the bladder wall, the bacteria create this protective layer. Administration of D-mannose helps to inhibit bacterial adhesion, reducing biofilm formation and thus facilitating clearance of the infection (21).

Etiology of Urinary Tract Infections

Although there are a variety of bacterial species that can cause UTIs, the most common organism isolated in both dogs and cats is *E coli*. In a 2003 study of 100 dogs with clinical signs of UTIs, urine was collected via cystocentesis. In these cases, bacteria were isolated from 38 samples. From these cultures 51 strains of bacteria were identified, with 76% of the positive samples resulting in a single strain of organisms and 23% yielding a mixed culture. *E coli* represented 23.5% of the organisms isolated. Other prevalent bacteria included *Streptococcus* spp., *Micrococcus* spp., *Staphylococcus* spp., *Klebsiella* spp., and *Proteus* spp. There did not seem to be a difference among the dogs with a positive culture based on age or gender (1). In a study conducted between January 1, 2010 and September 10, 2013, results were reviewed from positive aerobic bacterial cultures of urine collected via

cystocentesis in dogs. Of the 1636 bacterial isolates from 1028 dogs, *E coli* accounted for 52.4% of all the organisms (22). Seventy-four percent of the positive cultures were from females, with 90% of these from spayed females; of the remaining 26%, 80.6% were from neutered males.

In a 2008 review of 8,354 cases of canine UTIs, data collected from 1969-1995 were examined. The data showed a gender difference, with 58% of the bacterial isolates cultured from females. Over 3,400 microbes including bacteria and fungi were identified in the samples. Ten bacterial genera accounted for 96.3% of all isolates, with 44.1% of the total being *E coli*. In this review single isolates were responsible for over 72% of the UTIs (23).

As the studies above demonstrate, there is a wide variety of bacterial isolates, including many bacteria in the Enterobacteriaceae group. One factor in bacterial susceptibility to D-mannose is the presence of the FimH receptor; not all members of the Enterobacteriaceae, or even some strains within a species which tend to have the FimH receptors, actually possess them (12). Many bacteria in the Enterobacteriaceae group are regularly cultured in dogs with UTIs. These include *E coli*, *Enterobacter* spp., *Proteus* spp., and *Klebsiella* spp. A study in 2003 from the North Carolina State University Veterinary Teaching Hospital characterized the incidence of bacteria cultured from dogs with recurring UTIs. Of the bacteria isolated from dogs, there was a 47.4% incidence of *E coli*, 20.7% *Enterococcus* spp., 7.7% *Proteus* spp., and 5.9% *Klebsiella* spp. (18). Primary sources for *E coli* include contamination from the rectal and perineal areas (24). A review of UTIs in cats found that *E coli* was the most frequently isolated organism, representing the primary bacteria in 39% to 59% of the positive cultures (19). In a 2012 study of cats with chronic kidney disease, routine sampling found a predisposition to occult bacterial infections, with 18 of 25 cats affected. The study also identified *E coli* as the predominant bacteria (25).

Dosing

There is little confirmed information on proper dosing of D-mannose. Anecdotally, 500 mg of the powdered product per 9 kg body weight 3 times daily has been suggested (24). Another dosing method is to extrapolate from the human dose on the product label. Dosing pets 3 times a day can present a challenge with compliance, so many veterinarians recommend twice-daily administration. Based on the rapidity with which D-mannose is removed from the bloodstream into the urine in humans, more frequent dosing in dogs and cats may be indicated, albeit impractical.

There are several D-mannose combination products created specifically for the veterinary market or over-the-counter retailers. The range per dosing unit (soft chew, scoop, or tablet) is from 50 mg to 1000 mg. Often it is recommended that clients purchase the powder, as it is inexpensive and generally well accepted when sprinkled on moistened food. The compound itself tastes mildly sweet and inoffensive. It may be used in combination with water to supplement hydration and facilitate increased urination to help flush the bladder. In addition to the single-ingredient powder formulation, D-mannose is often a component in other pet supplements along with probiotics, cranberry, and other complementary nutrients.

Supportive Studies

Most of the clinical work and research done to determine the effectiveness of D-mannose has used adult women as the test subjects. Many studies support its use in women for UTI. A European survey found *E coli* to be the infective organism in 70% of cases, thus making potential use of D-mannose highly applicable (12). These studies in humans have generally been focused on recurrent UTIs, and in most of these, D-mannose helped decrease occurrences. The use of D-mannose helps lessen symptoms of dysuria, urgency, pain, and tenesmus, and increases quality of life (4). If the UTIs studied were recurrent, the interval between recurrences was extended with the use of D-mannose. The rate of recurrence in one study was 4.5% in women treated preventively with D-mannose, but 33% in those not given D-mannose (4). This 2016 Domenici study also found significant improvement in symptoms in women who received D-mannose prophylaxis. Additionally, there were no side effects noted (4). Similar results were found in a prospective study of men and women with multiple sclerosis and a history of recurrent UTI. D-mannose use significantly decreased the number of UTIs per month identified with the use of a dipstick by the patients (26).

In a 2014 study, 308 women were divided into 3 groups. After antibiotic clearance of documented UTI, the subjects were randomly assigned to a group given either D-mannose as a prophylactic, nitrofurantoin as a prophylactic, or no prophylaxis to determine the rate of recurrence. The women with no preventive treatment suffered a recurrence rate of 60.8%, those given D-mannose had a 14.6% recurrence rate, and subjects in the nitrofurantoin group had a recurrence rate of 20.4%. The difference in recurrence rates between mannose and nitrofurantoin was not significant, but both were significantly different from those receiving no prophylaxis (27). Patients in this study who received D-mannose also had significantly fewer side effects than those given nitrofurantoin. Another 2014 study showed similar results. Here,

60 women with a confirmed history of recurrent UTI were assigned to treatment with either D-mannose at a high dose for 2 weeks and then a lower dose for 22 weeks, or to a group receiving sulfamethoxazole and trimethoprim for 5 days. The average time for recurrence with the antibiotic group was 52.7 days, whereas the D-mannose group was 200 days (28). All 3 studies support the use of D-mannose to decrease the recurrence of, or extend the interval between, active UTIs. It is also noted in 2 of the above papers that there were no side effects of D-mannose observed. Therefore, D-mannose may help decrease incidences of urinary tract symptoms, acting in some cases as an effective method of prophylaxis.

In a 2015 study, D-mannose was shown to be helpful with acute bacterial cystitis as well. Patients included women either with symptoms of cystitis or who were asymptomatic but with a confirmed culture from a voided midstream sample. Those receiving D-mannose demonstrated significant improvement over baseline scores from a validated questionnaire, reporting fewer symptoms and improved quality of life (4).

A 2021 literature review of human studies provided a high level of evidence that the administration of D-mannose conferred a significant advantage with few, if any, side effects (11).



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D-mannose is often combined with other compounds, most often cranberry. Cure rates were significantly higher when a combination of cranberry and D-mannose was administered concurrently with antibiotics (29). In one study, cranberry plus D-mannose administered to women with sulfamethoxazole trimethoprim-resistant infections resulted in a persistent remission rate of 93% vs 55 % with placebo (29). Cranberry's proanthocyanidins may have different mechanisms of action, such as modifying the bacterial fimbriae or the shape of the organisms, possibly helping to decrease their ability to attach to the bladder wall. Compounds other than the proanthocyanidins, such as ursolic acid, may also impact *E coli's* gene expression to minimize biofilm production (30). The potential for synergism exists due to the different mechanisms of action of cranberry and D-mannose. When not given together, it was noted that D-mannose alone daily was a better preventive than proanthocyanidins (11).

Concrete, placebo-controlled studies in dogs and cats are lacking in veterinary medicine. While most studies are human-based, there is one in rats demonstrating that D-mannose was able to reduce bacteriuria significantly within 1 day (31). As with all non-companion animal research, it is unknown whether the results would be similar in the targeted species.

Potential Alternative Applications for D-mannose

In the body, D-mannose is primarily used for protein glycosylation. There have been other promising applications investigated, such as for the slowing of arthritis. An in vitro and in vivo rat study showed a decrease in the progression of degeneration of chondrocytes and an increase in cell proliferation. D-mannose also appears to downregulate catabolism and help slow the development of osteoarthritis (32). The sugar also inhibits inflammation by decreasing the products of neutrophil oxidative bursts and also by possibly decreasing activation of nuclear factor kappa B (33).

D-mannose may help to decrease tumor growth and enhance the cytotoxic effects of chemotherapy agents (34). It is thought that the mechanism of action for this inhibition of neoplasia may be due to impeding macrophage interleukin-1 β creation (35). It may also slow tumor growth by competing with neoplastic cells for glucose utilization (34). D-mannose has also been shown to decrease immunopathology by enhancing the production of T regulatory cells, which may have implications for controlling age-related and immune-related issues (36). This suppression of immune reaction may also assist in the prevention of autoimmune type 1 diabetes in humans (37).

Adverse Effects

Adverse effects are possible, although rarely reported. These include nausea, diarrhea, and abdominal discomfort. Caution is recommended for use with pregnancy and lactation (6). In one study, D-mannose use in pregnant mice resulted in offspring with eye defects (38).

Potential Drug Interactions

There are no known drug interactions with D-mannose.

Conclusions

UTIs are common in dogs and, although less common in cats, do occur, especially in felines with impaired renal function. When the UTI is due to outside factors, including immunosuppressive treatment, the presence of another disease, or anatomical abnormalities, preventive use of D-mannose could help manage these patients. Multiple UTIs in a patient may be classified as persistent, that is, the same strain of bacteria is able to elude the body's defenses and antibiotic therapy, or recurrent, in which the same or a different strain of bacteria recurs after being completely cleared by previous treatment. It is frequently difficult to distinguish between these 2 causes. In either case, *E coli* is most prevalent.

A potential long-term benefit of the use of D-mannose, since it does not alter the bacteria, could be a reduction in the number of antibiotic-resistant strains. Poor compliance when administering pharmaceuticals can result in low levels of the antibiotic in the bloodstream, which can promote bacterial genetic changes leading to resistance (39).

Not all bacteria are susceptible to the effects of D-mannose. Data is lacking on which bacteria express the mannose-binding capacity (24). Additionally, it is recommended that subclinical bacteriuria not be treated with antibiotics unless there is a concern for ascending infection, according to the antimicrobial use guidelines from the International Society for Companion Animal Infectious Diseases (16). These guidelines do not mention the use of complementary therapies such as D-mannose.

The use of D-mannose may help reduce the need for pharmacological intervention without interfering with it. Although there is less information to support the treatment of acute infections, there is support for its use to help decrease colonization and therefore reduce bacterial numbers available for induction of disease (12). D-mannose is synergistic with antimicrobial therapy (21). D-mannose has been found to have multiple beneficial

properties. It is synergistic with conventional medicines by not decreasing antibiotic effectiveness due to its physical mechanism of action in preventing bacterial attachment and thereby contributing to decreased colonization. Because of its benefits, low cost, and low incidence of adverse effects, it should be considered a standard preventive measure when formulating treatment plans for patients with recurrent UTIs.

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