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Evaluation of the Therapeutic Efficacy of Herbal Mixture, Cystolyberin, on E.coli J96-induced Bacterial Cystitis in Rats

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Abstract

Introduction: This study aimed to evaluate the effects of the herbal compound, Cystolyberin, on the treatment of bacterial cystitis in a rat model.

Materials and Methods: Twenty-eight male Sprague-Dawley rats were divided into four groups. Group 1 was the sham group, Group 2 served as the control, Group 3 received a short course of Cystolyberin, and Group 4 received an extended course. Bladder tissues and urine samples were collected after treatment. Urine culture results and histopathological findings were compared between the groups to assess the therapeutic effects of Cystolyberin.

Results: Urine cultures showed no E. coli in Groups 1 and 4, while 100% of Group 2 and 42.86% of Group 3 had persistent infection. Histopathological analysis revealed a significant reduction in bladder inflammation in Group 4 compared to Group 2. Additionally, there was a significant difference in lamina propria thickness across the groups. No significant differences were found for edema, vascular congestion, epithelial modification, urothelial integrity, or lymphocyte presence.

Conclusions: A 14-day course of Cystolyberin led to the eradication of E. coli in the rat model, demonstrating its potential as a treatment for bacterial cystitis. Further studies are needed to confirm these findings.

Key words: Medicine; herbal; cystitis; escherichia coli, experimental model.

Introduction

Urinary tract infections (UTIs) are prevalent global human illnesses, posing a substantial health concern in both community and hospital environments. Projections indicate that over 50% of women will experience at least one UTI in their lifetime due to their heightened susceptibility (1). UTIs consist of cystitis, an illness affecting the bladder or lower urinary tract, and pyelonephritis, an infection affecting the kidney or upper urinary tract. The most prevalent type of symptomatic UTI is uncomplicated cystitis—defined as a non-febrile lower UTI occurring in individuals without structural or functional urinary tract abnormalities—which comprises approximately 95% of all UTIs (2). Cystitis can be caused by numerous etiologic factors. UTIs are mostly caused by Escherichia coli and Klebsiella; however, other bacteria, such as gram-positive organisms and even fungi, have also been identified in numerous cases (3). E. coli is the primary bacterium responsible for causing UTIs in all groups of patients, accounting for 80–90% of all cases (4). While antibiotic therapy is generally effective in treating UTIs, there is a growing global issue of antibiotic resistance. Due to the need for prompt and efficient treatment, UTI management is frequently initiated empirically without conducting culture and sensitivity testing. The inappropriate use of antibiotics and insufficient attention to regional resistance patterns have contributed to the global spread of antimicrobial resistance, creating pathogens that are resistant to many antibiotics (5). Countries that strictly enforce antibiotic regulations tend to have fewer highly resistant strains, but still report significant rates of multi-drug-resistant and extended-beta-lactamase (ESBL)-producing strains of uropathogenic E. coli (UPEC) (6). In contrast, countries with less regulated antibiotic usage more frequently isolate such resistant strains. In clinical practice, prophylactic administration of antimicrobial agents is sometimes recommended to prevent recurrent UTIs, particularly in individuals with congenital anatomical

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abnormalities or those prone to frequent infections. However, continuous antimicrobial use carries the risk of fostering drug resistance and triggering drug-related side effects due to prolonged exposure. To circumvent the problems associated with the traditional use of antimicrobial agents for treating UTIs, herbal compounds have been employed as alternative therapeutic options, aiming to achieve comparable effectiveness. Several plant-based agents, such as Vaccinium macrocarpon (cranberry) and Arctostaphylos uva-ursi, have been traditionally used and studied for their ability to reduce bacterial adherence, acidity modulation, and anti-inflammatory effects in the urinary tract. Cystolyberin is a combination of herbal substances that are commonly associated with antibacterial and anti-inflammatory properties. Its components—Arctostaphylos uva-ursi, Vaccinium macrocarpon (cranberry), and D-mannose—are frequently used in supportive therapies for urinary tract health and have been included in this study based on their reputed therapeutic potential. This study aims to assess the in vivo therapeutic efficacy of the herbal compound Cystolyberin against UPEC-induced bacterial cystitis in a rat model. Specifically, we evaluated the compound's ability to reduce bacterial load through urine culture and its anti-inflammatory effects via histopathological analysis, comparing outcomes between short- and long-term treatment regimens.

Materials and Methods

Study design: Our hospital's Experimental Animals Laboratory provided the animals for the study. The study adhered to the guidelines for animal use and care in scientific procedures, and the Institutional Animal Care and Use Committee (IACUC) at our hospital approved the procedures and animal care (Approval Date and Number: 07/2018, 2018-21). We randomly assigned twenty-eight male Sprague-Dawley rats, with an average weight of roughly 300–350 g, to four groups. We provided all rats with a housing cage that maintained a consistent 12-hour day and night cycle, as well as unrestricted access to food and water throughout the entire trial. Group 1 consisted of the sham group, in which rats had surgery and had 0.6 ml of sterile saline injected into their bladders. They then received only drinking water for a period of 7 days. Group 2 served as the control group. The rats in this group underwent surgery and received an injection of 0.3 ml of sterile saline and 0.3 ml of E. coli J96, which contained 108 colony-forming units [CFU], into their bladder. We then gave them regular drinking water for a duration of 7 days. Group 3 and Group 4 were designated as the short-term and long-term treatment groups, respectively. In both groups, rats were administered 0.3 ml of sterile saline and 0.3 ml of the E. coli J96 strain, with a dosage of 108 colony-forming units [CFU]. Furthermore, rats in Group 3 and Group 4 were administered Cystolyberin at a dosage of 0.5 ml per 20 ml of water on a daily basis for 7 and 14 days, respectively. After the study concluded, we euthanized the rat models, collected urine samples for urine culture analysis, and took their urinary bladders for subsequent histopathological evaluation.

Operative technique: The rats received a single injection of 60 mg/kg ketamine and 10 mg/kg xylazine directly into their muscles to induce anesthesia after a 6-hour fast. We used the absence of a reflex response to paw pinching to assess the effectiveness of anesthesia. Next, we used electric clippers to shave the abdominal wall of each rat and cleansed the skin with a 10% solution of povidine iodine (Poviodine, Diagnokim Inc., Istanbul, Turkey). We made an incision on the lower abdomen wall, measuring approximately 1.5 to 2 cm in length. Afterwards, we separated the abdominal wall muscles using a method that involved careful and deliberate dissection. We isolated and exposed the urinary bladders. We extracted the urine from the bladder using a 2 ml syringe and then introduced a certain amount of sterile saline or E. coli into it. After repositioning the bladder, we sutured the abdominal muscles together using 3/0 absorbable polyglactin (Vicryl, Ethicon Inc., Somerville, NJ, USA), and closed the skin with 2/0 silk (Permahand Silk, Ethicon Inc., Somerville, NJ, USA). We disinfected the wounds with a 10% solution of povidine iodine. After the study concluded, we injected 60 mg/kg of ketamine and 10 mg/kg of xylazine into the muscles of the rats in each group to induce anesthesia. We subsequently exposed the bladders using the same method we used at the initiation of the investigation. We collected the urine in the bladder using a 1 ml syringe in a sterile environment and then sent it for culture. We then collected the bladders for further histological assessment. We preserved the bladder samples using a 4% solution of neutral formaldehyde and then placed them in paraffin blocks for embedding. Afterwards, the samples were manually sliced into paraffin slices that were 4-6 µm thick using a microtome. After dewaxing, we treated the sections with hematoxylin and eosin (H&E). The collected urine samples were

Table 1: Comparison of the histopathologic findings of the rat bladders and urine culture test results obtained in all groups

		Group 1		Group 2		Group 3		Group 4		p
Edema	None	3	60.00%	0	60.00%	1	14.29%	3	50.00%	
	Mild	2	40.00%	3	40.00%	4	57.14%	3	50.00%	
	Moderate	0	0.00%	2	0.00%	2	28.57%	0	0.00%	0.208
Vascular congestion	None	1	20.00%	0	20.00%	2	28.57%	3	50.00%	
	Mild vascular dilatation	4	80.00%	1	80.00%	4	57.14%	2	33.33%	
	Commonly present in part of lamina propria	0	0.00%	3	0.00%	1	14.29%	1	16.67%	
	Commonly present in the entire lamina propria	0	0.00%	1	0.00%	0	0.00%	0	0.00%	0.150
Inflammation	None	5	100.00%	0	100.00%	3	42.86%	3	50.00%	
	Mild	0	0.00%	0	0.00%	2	28.57%	3	50.00%	
	Moderate	0	0.00%	5	0.00%	1	14.29%	0	0.00%	
	Severe	0	0.00%	0	0.00%	1	14.29%	0	0.00%	0.002
Epithelial alteration	No dysplasia / reactive changes	4	80.00%	2	80.00%	3	42.86%	5	83.33%	
	Dysplasia / reactive changes	1	20.00%	3	20.00%	4	57.14%	1	16.67%	0.272
Urothelial epithelium lining	Double	1	20.00%	0	20.00%	1	14.29%	0	0.00%	
	Triple	4	80.00%	2	80.00%	5	71.43%	6	100.00%	
	Quadruple	0	0.00%	3	0.00%	1	14.29%	0	0.00%	0.106
Presence of lymphocytes in the urothelium	No	4	80.00%	1	80.00%	3	42.86%	2	33.33%	
	Yes	1	20.00%	4	20.00%	4	57.14%	4	66.67%	0.252
Positive urine culture	No	5	100.00%	0	100.00%	4	57.14%	6	100.00%	
	Yes	0	0.00%	5	0.00%	3	42.86%	0	0.00%	0.001

Categorical data are presented as count (percentage within group). p-values were calculated using Chi-square, as appropriate.

Table 2: Comparison of measured thickness of lamina propria (in micrometers) obtained from histopathologic evaluation in all groups

	Group 1	Group 2	Group 3	Group 4	p
Thickness of lamina propria (µm)	57.2±11.71	96.8±31.26	77.43±26.63	55.67±14.05	0.025

Values are presented as Mean ± SD. Although a non-parametric test (Kruskal-Wallis) was used for comparison, mean and SD are reported due to data availability. Overall p-value was calculated using the Kruskal-Wallis test. Pairwise comparisons were conducted using Dunn's post-hoc test.

preserved and transported at a temperature of 4 °C and subjected to microbiological analysis. We subsequently euthanized the rats using a high dosage of anesthetic.

Herbal agent: Gelatin capsules containing Cystolyberin, a plant-derived botanical blend, are available for purchase. Each capsule contains specific amounts of the following plants: Arctostaphylos uva-ursi (250 mg) and Vaccinium macrocarpon (100 mg), together with a simple sugar called D-mannose (250 mg). Furthermore, magnesium ions of fatty acids (E 470 b) compose cystolyberin. There are 30 capsules in each blister.

Microbiological evaluation: We conducted the urine cultures by introducing 0.01 ml of rat urine onto Mac Conkey agars and evenly spreading it across the entire surface of the plate. We then incubated the inoculated plates aerobically at 35°C

for 24 hours to allow for the growth of colonies, which we then counted to determine their quantity.

Histopathological examination: A skilled genitourinary pathologist exclusively performed the examinations. The samples were examined using light microscopy to evaluate different factors. The factors evaluated included the presence and severity of edema (none, mild, moderate, and severe), vascular congestion (none, mild, commonly present in part of the lamina propria, commonly present in the entire lamina propria), the level of inflammation (none, mild, moderate, and severe), the presence of reactive changes or dysplasia in the epithelial cells, the urothelial epithelium lining (double, triple, quadruple), the presence of lymphocytes in the epithelium, and the thickness of the lamina propria (measured in micrometers).

Statistical analysis: We conducted the data analyses and statistical evaluation using the Number Cruncher Statistical System 2007 Statistical Software (NCSS, LLC, Kaysville, UT, USA). We presented the data as the mean value plus or minus the standard error of the mean. We statistically compared the groups using the Kruskal-Wallis multiple comparison test, and compared the subgroups using Dunn's multiple comparison test. The examination of qualitative data involved the utilization of Fisher's exact test and chi-square test. We deemed the disparities statistically significant at a p-value below 0.050. Dunn's multiple comparison test was used following Kruskal-Wallis to address multiple comparisons; the test inherently adjusts p-values to control for Type I error.

Results

We examined the bladder tissue samples to determine if injecting E. coli caused any inflammatory changes. The results revealed a significant difference in the level of inflammation and the thickness of the lamina propria between the groups ($p = 0.002$ and $p = 0.025$, respectively), as presented in Tables 1 and 2. Dunn's multiple comparison test demonstrated a statistically significant increase in the presence of moderate inflammation in Group 2 compared to Group 1 ($p = 0.001$) and Group 4 ($p = 0.004$). Additionally, the measurement of lamina propria thickness was significantly higher in Group 2 compared to Group 1 ($p = 0.009$) and Group 4 ($p = 0.022$), respectively. However, there were no statistically significant differences seen in terms of the extent of swelling, blood vessel congestion, changes in the outer layer of cells, lining of the urinary tract, and the presence of immune cells in the outer layer of cells (Table 1). In addition, the urine culture test produced negative results for all rats in both group 1 and group 4. Nevertheless, Group 2 exhibited positive urine cultures in 100% of rats, while Group 3 had positive urine cultures in 42.86% of rats ($p = 0.001$). The presence of UTI is a crucial factor in this investigation.

Discussion

UTIs are highly widespread infections that affect a significant portion of the global human population. Bacterial cystitis is the predominant kind of UTI, accounting for 95% of all symptomatic cases. It is more prevalent in women. While UTIs can be caused by various pathogens, including Staphylococcus, Klebsiella, Enterobacter, Enterococci, and fungus species, the primary causative UPEC (1-4). Although antibiotic therapy is generally efficacious in managing UTIs in various clinical contexts, the escalating problem of antibiotic resistance has emerged as a substantial worldwide public health issue. Due to the need for prompt and efficient treatment, UTI treatment is commonly begun empirically without doing culture and sensitivity testing. The improper utilization of antibiotics and disregard for local resistance patterns has led to the global establishment of antibiotic resistance in bacteria, resulting in the proliferation of bacterial pathogens with multiple resistance traits (5). Although nations with strict antibiotic protocols do not currently have a large prevalence of highly resistant strains, countries with less regulated antibiotic usage often face UPEC bacteria that are resistant to many drugs and produce ESBL (6). Initially, ampicillin, trimethoprim, sulfur-based antimicrobials, or tetracyclines were the only agents that showed resistance (7). Recently, researchers have observed that ESBL manufacturers are not only resistant to the majority of -lactam antibiotics, but they have also acquired resistance to aminoglycosides and fluoroquinolones (8). Aside from the prevalence of antibiotic resistance, the use of antibiotics to treat UTIs can also disrupt the balance of microorganisms in the intestinal microbiota. When the regular microorganisms in the body are disrupted, the body's ability to prevent the growth of resistant microorganisms, such as C. difficile, can decrease, leading to uncontrolled proliferation. Resistant potential pathogens have the ability to colonize again and can then disseminate to other regions of the body, leading to the development of serious diseases (9). In addition, antibiotic consumption is associated with

numerous unpleasant effects, such as nausea, vomiting, abdominal pain, skin rash, and headache, among others. Given the constraints related to the use of antibiotics, herbal medications can serve as a more favorable alternative approach for preventing and treating UTIs (10). Since ancient times, people have used medicinal plants for their advantageous properties in the management of certain ailments. Despite the significant progress in contemporary medicine, people still view medicinal plants as indispensable in healthcare. In recent years, herbal medicines have become increasingly popular, not just in underdeveloped countries but also in industrialized countries. Phytotherapeutic agents are standardized herbal treatments that contain complicated mixes of one or more plants. People use them to treat various disorders. Multiple studies have demonstrated the effectiveness and ability of different herbal agents and phytotherapeutics to inhibit the growth of microorganisms. These can be used as substitutes for antibiotics in the treatment of UTIs. Cranberry, namely Vaccinium macrocarpon, is the most widely recognized natural remedy for treating UTIs. This substance's high concentration of hippuric acid, which increases urine acidity, drives its antibacterial activity. Further examination of this natural substance has also unveiled its potent anti-adhesive characteristics (11). Stothers et al. conducted a one-year randomized trial study to evaluate the efficacy of cranberry products in reducing UTIs among a cohort of 150 sexually active women. The study found that consuming cranberry products on a regular basis led to a reduction in the use of antibiotics compared to a placebo, as well as a statistically significant decrease in the number of recurring symptomatic UTIs (12). An additional meta-analysis of 10 studies that adhered to the Cochrane criteria for inclusion examined the advantages of cranberry juice and cranberry pills in comparison to a placebo control. The study showed that cranberry effectively decreases the occurrence of UTIs throughout a span of 12 months (13). Researchers conducted a randomized-controlled experiment to evaluate the anti-adherence impact of cranberries in bladder cases of E. coli infection. The study found that consuming cranberries led to a considerable decrease in bacterial adhesion, and this decrease was dependent on the dosage (14). Berberine, a plant alkaloid, has been a long-used herbal substance. Several plant species, such as Hydrastis canadensis (goldenseal), Coptis chinesis (Coptis or goldenthread), Berberis aquifolium (Oregon grape; Mahonia aquifolium), Berberis vulgaris (barberry), and Berberis aristata (tree turmeric), contain berberine in their roots, rhizomes, and stem bark. Berberine extracts demonstrate significant antibacterial effectiveness against a wide variety of organisms, including bacteria, viruses, fungi, protozoa, helminths, and chlamydia (11). An experimental analysis revealed that berberine, extracted from Berberis aquifolium, has antibacterial characteristics. The bacteria examined in this study include both susceptible and resistant strains of E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, and Bacillus subtilis (15). A separate in vitro investigation has shown that berberine possesses anti-adhesive properties against uropathogenic E. coli. Under an electron microscope, we found fimbrial filaments covering the bacteria after growing it in a culture medium for eighteen hours. The production of fimbriae was completely stopped when E. coli was grown for 18 hours with 200 mcg/mL berberine sulfate present (16). Sharm et al. conducted a study on seventeen Indian folklore medicinal plants to test their effectiveness against uropathogens that are resistant to multiple drugs. The study found that ethanol extracts from some plants, like Terminalia chebula, Ocimum sanctum, Azadirachta indica, and Punica granatum, could kill bacteria that cause infections in the urinary tract, like E. coli, Pseudomonas aeruginosa, Enterococcus faecalis, and Klebsiella pneumoniae (17). Agathosma betulina, commonly known as buchu, is a longstanding herbal remedy for UTIs. The leaves of this plant contain a variety of phenolic chemicals that possess both antibacterial and antidiuretic qualities. We conducted an investigation to demonstrate the antimicrobial impact of the ethanol extract from A. betulina. The investigation has shown that the ethonal extract of the plant exhibits antibacterial activity against E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, S. aureus, Staphylococcus saprophyticus, and E. faecalis (18). Additional research on the extracts derived from A. betulina revealed its ability to prevent adhesion by interacting with T24 cells (19). Herbs like Althea officinalis, Arctium lappa (burdock), Elymus repens (couchgrass), Hydrangea aborescens (hydrangea), Mentha piperita (peppermint), Juniperus communis (juniper), and Zea mays (corn silk) have also been shown to help treat UTIs. However, a comprehensive comprehension of their methods of action necessitates additional scientific investigation (10). The botanical extracts of uva-ursi and Vaccinium macrocarpon (Cranberry) form the basis of Cystolyberin, a

phytotherapeutic remedy. The Arctostaphylos plant's leaves yield the herbal extract known as uva ursi. People widely use it as a natural remedy for UTIs. Urine's alkaline pH produces arbutin, the substance's direct antibacterial activity. To get optimal outcomes, it is necessary for the pH of urine to be alkaline. Patients should exert effort to maintain a high urine pH through the assistance of a vegetable-based diet. Researchers attribute the antibacterial action of aqueous uva ursi extracts to their ability to alter the surface properties of microbial cells (7). Researchers have discovered that uva ursi possesses antidiuretic effects. An animal study found that uva ursi significantly increased urine production, without affecting the excretion of sodium and potassium (20). Cyanolyberin includes D-mannose, a simple sugar, as a highly effective supplement for treating and preventing UTIs. Several fruits contain D-mannose, an endogenous sugar. It inhibits the attachment of specific bacterial strains to the uroepithelial cells of the bladder. In vitro research has found a mannose-specific lectin on the surface of adherent strains of E. coli (21). Another study examined the mechanism of adhesion and found that D-mannose is the main receptor site on bladder cells for UPEC (22). The current study shows that giving the herbal preparation mixture Cystolyberin for a short time or a long time may have an effect on the treatment of E. thecoli cystitis. Long-term consumption yielded a more advantageous consequence. Cystolyberin not only effectively eliminated uropathogenic bacteria but also reduced inflammation of the bladder mucosa. The findings indicate that the use of cystolyberin may have positive effects in the management of bacterial cystitis.

Study limitations: This study has several limitations. The findings are based solely on one strain of E. coli, so the efficacy of Cystolyberin against other uropathogens remains unknown. Additionally, the study duration was limited to 14 days, and long-term effects or potential side effects were not evaluated. As the study was conducted on animals, further clinical trials in humans are necessary to confirm its safety and effectiveness. Furthermore, the sample size per group was limited (n=7), which may reduce the statistical power of the study, particularly for variables with high variability or subtle inter-group differences. The statistical methods used in this study, including the application of the Kruskal-Wallis and Dunn's tests as well as categorical data analyses, were selected with consideration of non-parametric data characteristics and reviewed for methodological consistency.

Conclusions

Cystolyberin can serve as a substitute therapeutic drug for the management of UTIs. Cystolyberin not only eliminates the E. coli J96 strain but also effectively reduces irritation of the bladder mucosa. Additional clinical trials are required to assess the safety and effectiveness of cystolyberin therapy for treating UTIs in persons.

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Ethical approval: Our hospital's Experimental Animals Laboratory provided the animals for the study. The study adhered to the guidelines for animal use and care in scientific procedures, and the Institutional Animal Care and Use Committee (IACUC) at our hospital approved the procedures and animal care (Approval Date and Number: 07/2018, 2018-21).

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