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Original Research Article

Clinical Pharmacology for better medical treatment

Clinical Trial To Assess The Usefulness Of CV-HFU01 Tablets In Management Of Recurrent Urinary Tract Infection

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Abstract: Urinary Tract Infections (UTIs) are a major reason of illness in infant boys, older men and females of all ages. Severe sequelae embrace persistent recurrences, pyelonephritis with sepsis, renal damage in young children, preterm birth and complications caused by frequent usage of antimicrobial agents including high-level antibiotic resistance and *Clostridium difficile* colitis. Thus, a test product "CV-HFU01" was developed by Climic Health Pvt. Ltd, with the objective to assess its usefulness for the management of recurrent UTI. It was an open label, single arm, prospective, interventional clinical study. The subjects were advised to consume 1 tablet of CV-HFU01 twice daily orally before meal with water for 3 months. The change in symptoms of UTI; Patients Global Assessment; Physician's global Assessment; safety of CV-HFU01 tablets was determined by assessing the adverse events and tolerability of CV-HFU01 tablet. CV-HFU01 was significantly effective in relieving symptoms associated with recurrent UTI like change in symptoms like burning micturition, intermittent urination, pain during urination and other symptoms of UTI. The results revealed that subjects undergoing the treatment duration of 90 days but in first 30 days 80% subjects presented complete recovery from all the symptoms related to UTI. CV-HFU01 was safe and effective alternative in the management of recurrent UTI.

Keywords: CV-HFU01, Recurrent UTI, Single arm, Open label, Patients Global Assessment

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1. INTRODUCTION

Urinary tract infection (UTI) is a collective term that describes any infection involving any part of the urinary tract, namely the kidneys, ureters, bladder and urethra. The urinary tract can be divided into the upper (kidneys and ureters) and lower tract (bladder and urethra).Urinary tract infections (UTIs) are some of the most common bacterial infections, affecting 150 million people each year worldwide. In 2007, in the United States alone, there were an estimated 10.5 million patient visits for UTI symptoms (constituting 0.9% of all ambulatory visits) and 2–3 million emergency department visits. Currently, the societal costs of these infections, including health care costs and time missed costs from work, are approximately US $3.5 billion per year in the United States alone. UTIs are a significant cause of morbidity in infant boys, older men and females of all ages. Serious sequelae include frequent recurrences, pyelonephritis with sepsis, renal damage in young children, preterm birth and complications caused by frequent usage of antimicrobial agents including high-level antibiotic resistance and Clostridium difficile colitis.[1-2] *Escherichia coli* and *Staphylococcus saprophyticus* account for about 80% of community-acquired uncomplicated urinary infections (UTI), particularly in women under 50 years of age. *E. coli* is a Gram-negative commensal of the distal colon which also harbors other anaerobic bacteria, including Bacteroides and Bifidobacteria. Uropathogenic E. coli differs from intestinal pathogenic E. coli with regard to the presence of specific virulence factors. Among the various serotypes of E. coli, 01, 02, 04, 06, 07, 08, 016, 018, 025, and 075 are commonly recovered from patients with UTI. About 80% of uropathogenic E. coli express P fimbriae which anchor to the glycolipid of the outer membranes of urothelial cells localized in the kidney. P fimbriae are frequently associated with cases of acute pyelonephritis. Another important virulence factor is Type 1 fimbriae. These are very important in the mechanism of bacterial adhesion to the uroepithelium. They are comprised of several subunits, the most important is an adhesion protein known as FimH which plays a principal role in the pathogenic mechanism of E. coli at the level of the urinary tract. It mediates both cellular invasion of E. coli and adhesion to mannose-containing glycoproteins. *In vivo* and *in vitro* studies have shown that the pathogenicity of E. coli is mainly related to mechanisms of colonization and invasion of the bladder epithelium and the ability to form intracellular bacterial communities. FimH enables uropathogenic E. coli to escape the innate immune response by internalization within urothelial cells, mediated by the activation of host signal transduction cascades via protein tyrosine kinases, phosphoinositide-3 kinase, and localized host actin cytoskeletal rearrangements. After invasion, E. coli is harboured within vesicles inside infected urothelial cells, from which it cannot be expelled. FimH also plays a role in the modulation of epithelial apoptosis and exfoliation in the mechanisms of cytoplasmic replication. Therefore, it is a very powerful factor in invasion and virulence. When FimH is not present, the uroepithelium is usually able to clear E. coli colonies via expulsion and mechanisms of the cellular immune response. S. saprophyticus is a common UTI pathogen in younger women. Most UTI caused by Candida spp are associated with the use of indwelling urinary devices, including Foley catheters, internal stents, and percutaneous nephrostomy drains. Diabetics are particularly prone to fungal UTI. Normally this kind of infection is acquired by patients with severe neutropenia, drug abuse, recent surgery (chest, abdomen), and systemic infection. [3-6] Clinically, UTIs are categorized as uncomplicated (acute) or complicated (chronic). Uncomplicated UTIs typically affect individuals who are otherwise healthy and have no structural or neurological urinary tract abnormalities; these infections are differentiated into lower UTIs (cystitis) and upper UTIs (pyelonephritis). Several risk factors are associated with cystitis, including female gender, a prior UTI, sexual activity, vaginal infection, diabetes, obesity and genetic susceptibility. Complicated UTIs are defined as UTIs associated with factors that compromise the urinary tract or host defence, including urinary obstruction, urinary retention caused by neurological disease, immune suppression, renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as calculi, indwelling catheters or other drainage devices. UTIs are caused by both Gram-negative and Gram-positive bacteria, as well as by certain fungi. The most common causative agent for both uncomplicated and complicated UTIs is uropathogenic Escherichia coli (UPEC). For the agents involved in uncomplicated UTIs, UPEC is followed in prevalence by Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, group B Streptococcus (GBS), Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus and Candida spp. For complicated UTIs, the order of prevalence for causative agents, following UPEC as most common, is Enterococcus spp., K. pneumoniae, Candida spp., S. aureus, P. mirabilis, P. aeruginosa and GBS9. [7-9]

1.1 Uncomplicated versus complicated UTI

A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease; this increases the risk of the outcome of a UTI being more serious than expected, as compared to its occurrence in individuals without any identified risk factors (i.e. uncomplicated UTI). The European Association of Urology's classification system for UTIs, known as ORENUC, is based on the clinical presentation of the UTI and its associated host risk factors (Table 1). In adults, uncomplicated UTIs fall under categories O, R and partially E, while complicated UTIs are mainly in categories N, U and C.[10]

Table 1. ORENUC classification based on clinical presentation of urinary tract infection (UTI) and risk factors (RFs)

Type	Category of RF	Example
O	No known/associated RF	Healthy premenopausal women
R	Recurrent UTI RF, but no risk of severe outcome	Sexual behaviour and contraceptive devices Hormonal deficiency postmenopause Secretory type of certain blood groups Controlled diabetes mellitus
E	Extra-urogenital RF, with risk of more severe outcome	Pregnancy Male gender Badly controlled diabetes mellitus Relevant immunosuppression Connective tissue diseases
N	Nephropathic disease, with risk of more severe outcome	Relevant renal insufficiency Polycystic nephropathy
U	Urological RF, with risk of more severe outcome, which can be resolved during therapy	Ureteral obstruction (i.e. stone, stricture) Transient short-term urinary tract catheter Asymptomatic bacteriuria Controlled neurogenic bladder Urological surgery
C	Permanent urinary catheter and non-resolvable urological RF, with risk of more severe outcome	Long-term urinary tract catheter treatment Non-resolvable urinary obstruction Badly controlled neurogenic bladder

1.2 Recurrent UTI

Recurrent UTIs are symptomatic UTIs that follow the resolution of an earlier episode, usually after appropriate treatment. They are common among young, healthy women even though these women generally have anatomically and physiologically normal urinary tracts. Recurrent UTIs can be diagnosed clinically without performing a urine culture, although urine cultures are essential in management. For women with recurrent UTIs, imaging of the upper urinary tract and cystoscopy are not routinely recommended for evaluation. However, they should be performed without delay in patients with atypical symptoms, such as obstructive symptoms or presence of haematuria after resolution of infection. [11] Community-onset urinary tract infection (UTI) disproportionately affect females, however, routine and complicated UTIs in male patients are neither nonexistent nor benign. Males at the extremes of age, namely infants and the very elderly, exhibit increased incidence of UTI. Further, complicated UTI commonly manifests in males with urodynamic problems (*e.g.,* spinal cord injury or neurogenic bladder), indwelling urinary catheters, immunosuppression, and/or structural abnormalities. Importantly, while female cases of complicated and upper-tract UTI (pyelonephritis) outnumber male cases overall, males carry an increased risk of mortality from these infections. Millions of males also suffer from acute and chronic bacterial prostatitis. In total, UTIs comprise debilitating diseases with substantial morbidity and an appreciable mortality specific to males. Of note, uropathogenic *Escherichia coli* (UPEC) is the predominant cause of UTI in both sexes, causing >80% of community onset UTI, approximately 25% of hospital-acquired UTI, and >70% of infectious prostatitis. [12-13] The incidence of urinary tract infection increases with age. During the first few months of life, the incidence of urinary tract infections in male exceeds that of females. From the first year, both first time and recurrent urinary tract infection is much more common in females. The female urethra appears to be particularly prone to colonization because of its proximity to the anus. Men's risk for UTI increases with age, men become more susceptible to UTIs after 50 years of age, when they are more likely to develop prostate problems due to loss of prostate fluid. Enlarged prostate gland can also impede and slow the flow of urine, thus raising the risk of infection. It is observed that men who are not circumcised tend to also be more prone to developing UTIs because these bacterial build up much more easily in the folds of the extra skin on the penis thereby making them more susceptible to developing UTIs. [14-15] In premenopausal women, 90% of the vaginal flora is Lactobacilli, which protects the system against colonization with uropathogens such as E. coli, with estrogen loss at menopause, it results in the thinning of the vaginal epithelium and decreased amount of glycogen. The resulting environment is usually hostile to Lactobacilli thereby decreasing their numbers. Biological changes due to menopause put these women at particular risk of contracting both primary and recurring UTIs because with estrogen loss, the walls of the urinary tract becomes weak and as such it reduces its ability to resist bacteria colonization.[16] Most uncomplicated UTIs are treated in the outpatient setting. However, patients who present with fevers or systemic symptoms of infection (e.g., systemic inflammatory response with a suspected urinary source) should be hospitalized and treated with parenteral antibiotics. Initial therapy is based on the local susceptibility patterns of E. coli and other uropathogens. Nitrofurantoin is recommended for the treatment of cystitis, which is highly active against E. coli, with 0.9% resistance among female. Serious adverse effects, including renal failure in infected women and older have been reports for nitrofurantoin. Trimethoprim/Sulfamethoxazole and Trimethoprim/sulfamethoxazole remains an highly effective agent for the treatment of uncomplicated cystitis, with cure rates of 90%–100%. It is also effective in the treatment of UTIs in men. Fluoroquinolones (e.g., levofloxacin or ciprofloxacin) are recommended for the treatment of uncomplicated pyelonephritis and complicated UTIs, including urosepsis when the local resistance is less than 10%. Alternatives to fluoroquinolones such as nitrofurantoin or amoxicillin/clavulanate are recommended for uncomplicated UTIs. According to the manufacturer's package insert, about 20% of moxifloxacin is excreted unchanged in the urine, and moxifloxacin is currently not recommended for the treatment of UTIs. Fosfomycin Trometamol has in vitro activity against most Enterobacteriaceae spp. including ESBL-producing isolates and Enterococcus spp. (regardless of vancomycin susceptibility). Oral β-Lactam antibiotics (e.g., amoxicillin/clavulanate, cefaclor, cefdinir, cefpodoxime, and

ceftriaxone) reports lower efficacy than with fluoroquinolones and trimethoprim/sulfamethoxazole. β-Lactam antibiotics are considered alternative agents in managing uncomplicated UTIs. [17-20] Urinary tract infection is commonly treated with prescription antibiotics. However, it is increasingly recognized that using antibiotics frequently may contribute to recurring UTIs and increased dependency on antibiotic use may further weaken the immune system. Natural remedies can provide an effective alternative to prescription medications and their side effects. Although modern antibiotics are being used in UTIs, urinary tract infections can be quickly and easily treated with an herbal treatment with no side effects. Herbs known for the management of urinary tract Infections and other urinary disorders divided in important categories: (a) Urinary antiseptic and anti-adhesion herbs like Juniperus spp., *Vaccinium macrocarpon*, *Salvia officinalis, Punica granatum, Tribulus terrestris, Terminalia chebula, Ocimum sanctum, Cinnamomum cassia, Azadirachta indica* and *Ocimum sanctum*, which are effective against major urinary tract pathogens namely *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Enterococcus faecalis* (d) Bladder protectives that control bladder and protect from infections comprising of *Equisetum arvense, Hydrangea petiolaris and Zea mays* (e) Kidney care for instance, *Boerhaavia diffusa, Eupatorium purpureum, Agropyron repens* and *Berberis vulgaris* and (f) Herbs for symptoms of benign prostatic hyperplasia, most notably *Serenoa repens* and *Prunus africana*. All these herbs are discerned to know different type of phytoconstituents and show potential in the treatment of urinary disorders and could be alternative to uropathogen resistance to the antibiotic during a UTI. [20-22]Climic Health Pvt. Ltd. has developed CV-HFU01 tablets for effective for the management of recurrent UTI. Hence, aim of this research focuses on the assessment of safety and efficacy of CV-HFU01 tablets in patients with recurrent UTI.

2. MATERIALS AND METHODS

2.1 Product Description

The ingredients of the test product was tabulated in the table 2. The test product was made available in the pack size of 60 tablets per container with seal.

Table 2. Product Description

Sr. No.	Common Name of Ingredients	Botanical Name of Ingredients	Quantity w/w
1	Shodhit Guggul	*Commiphora mukul*	*250 mg*
2	Gokhru Panchang	*Tribulus terrestris*	*125mg*
3	Sounth	*Zingiber officinale*	*15 mg*
4	Marich	*Piper nigrum*	*15 mg*
5	Pippali	*Piper longum*	*15 mg*
6	Harad	*Terminalia chebula*	*15 mg*
7	Baheda	*Terminalia bellirica*	*15 mg*
8	Awala	*Emblica officinalis*	*15 mg*
9	Nagarmotha	*Cyperus rotundus*	*15 mg*
10	Punarnava	*Boerhaavia diffusa*	*10 mg*
11	Varun Chhal	*Crataeva nurvala*	*10 mg*

All the ingredients were mixed and the blend was compressed to form uniform tablets using tablet compression machine. These tablets were packed in food grade HDPE containers of 30 Tablets. The detailed method of manufacturing was not reported due to trade secrecy and restrictions.

2.2 Ethics

The study was initiated after obtaining written approval from Independent patients and individuals .Prior approval from the Institutional Ethics Committee (IEC) was also obtained for this study. The study was conducted as per approved protocol and as per Good Clinical Practices (GCP) guidelines given by AYUSH in March 2013. After getting approval from the ethics committee, the study was registered on the website of Clinical Trial Registry of India (CTRI). The CTRI number of the study is CTRI/2019/04/018452, registered on 08/04/2019. Subjects were enrolled after registration of the study on CTRI website.

2.3 Study design

It was an open label, single arm, prospective, interventional clinical study.

2.4 Study Objectives

The primary objective of the study was to evaluate change in symptoms like Burning micturition, intermittent urination, pain during urination and other symptoms of UTI. Evaluating the patient's Global Assessment; Physician's Global Assessment; the safety by noticing adverse events and tolerability of CV-HFU01 tablets in patients with recurrent UTI were the secondary objectives of the study.

2.5 Subject Recruitment Plan

33 subjects were recruited in the study to get 30 completers (30 in each group) at the end of the study. Subjects who were ready to provide written informed consent and ready to provide regular follow ups till the completion of the study and met inclusion and exclusion criteria were recruited in the study. Precautions were taken not to recruit the subjects belonging to possible vulnerable groups.

2.6 Subject inclusion Criteria

Subjects of either sex of age 18 to 60 years (both inclusive) having subclinical (asymptomatic bacteriuria) and or recurrent UTI (2-3 episodes of UTI in the last 12 months) were included in the study.

2.7 Subject Exclusion Criteria

Subjects with the first episode of symptomatic active UTI; known history of hyperoxaluria/known renal oxalate stone

formers were not included in the study. Subjects who were pregnant and or lactating and the pediatric age group were excluded from the study.

2.8 Dosage and Treatment Duration

One tablet of CV-HFU01 twice daily orally before meal with water for 3 months for the subjects with recurrent UTI were administered to subjects. Subjects were advised lifestyle modifications (nutritious diet, exercise etc.) and were called for follow up at Day 30, Day 60 and Day 90 after consumption of medication.

2.9 Study Visits/ Follow Ups

Screening Visit (Up to Day- 5), Baseline Visit (Day 0), Visit 1 (Day 30), Visit 2 (Day 60), Visit 3 (Day 90). Subjects were allowed to come for follow up either 5 days prior or after the scheduled follow up visit time. A screening window of up to 5days was kept, in case if there was a delay in the availability of tests reports or in case few tests needed to be repeated.

2.10 Study Assessments

2.10.1 Assessment of efficacy[23]

The primary efficacy was evaluated by assessing the improvement in symptoms like burning micturition, intermittent urination, pain during urination and other symptoms of UTI from baseline to day 90 i.e. end of study. The secondary efficacy evaluated was assessing the patients Global Assessment, Physician's Global Assessment, safety of CV-HFU01 tablets by observing adverse events and evaluating the tolerability and safety of CV-HFU01 tablets in patients with recurrent UTI.

2.10.2 Assessment of Physician's and Subject's Clinical Global evaluation for overall efficacy

Investigator and subject provided ratings for efficacy, whether or not, it was entirely due to product treatment compared to subject's condition at admission to the study and how much had he / she changed on completion of the study.

2.10.3 Assessment of Safety[24]

Safety was assessed by clinical review of all safety parameters, including the adverse event reporting, as applicable; vital signs (Pulse, Respiratory rate, Temperature, BP) (data not presented here); assessment of Overall Safety and Tolerability of the products by the physician and subject on global assessment scale by the investigator and by subject.

2.10.4 Study procedures

Subjects identified as having recurrent UTI were screened for recruitment. Screening of 30 subjects completed at the end of the study. On screening visits (up to day -5), a written informed consent was obtained from subject for his/ her participation in the study. Subject underwent physical and systemic examinations. Subject's medical and surgical history was taken. Subject's current medication if any was noted in the Subject was called next day morning on an empty stomach for laboratory investigations. Subject's data on symptom gradation of UTI were performed. Subject's data regarding conventional treatment were recorded. Also subjects were advised to refrain from any Nutraceutical, Ayurvedic, homeopathic, Siddha, Unani etc. treatment for urinary tract infection. On baseline visit, subjects were recruited if he/she met all the inclusion criteria. Subjects underwent general and systemic examinations and symptom gradation. Subjects were instructed to consume CV-HFU01 tablets before meal. Subjects were advised to follow visit schedule i.e. Day 30, 60 and 90 respectively after consumption of CV-HGU01 tablets. Subjects were given medication packed in single HDPE container each containing 60 tabs. On follow up visits (Day 30 and 60), all the subjects were closely monitored for any Adverse Events. Subjects were advised not to consume alcohol, caffeine, and nicotine during the study period. Subjects underwent general and systemic examinations, clinical symptom gradation. On every follow up visit, parameters like symptom gradation with quality of life assessment were assessed. The container provided to the subject on the previous visit was collected and remaining drug was counted to check missed dosage. Subjects who missed dosing partially or completely were treated as drop outs. On final Visit (Day 90), all the subjects were closely monitored for any Adverse Events. If the subject had AE/SAE, the details of the incident were documented in the source document and CRF. SAE, if any, was reported to the IEC in a SAE reporting form. Rescue medication used, if any, was recorded in the CRF. On Day 90 visit, symptom gradation with quality of life was assessed. On Day 90, subject's global evaluation for overall improvement and Investigator's global evaluation for overall improvement were done. Subject's tolerability towards CV-HFU01 tablets was assessed. Subjects were advised not to consume alcohol, caffeine, and nicotine during the study period.

3. STATISTICS

Primary endpoints taken under consideration were symptoms associated with recurrent UTI. Change in subjective clinical signs and symptoms from baseline to each visit and end of therapy was analyzed and tested by Chi Square test using statistical software SPSS 10.0. The analysis of secondary efficacy were percentage change in subjective clinical signs and symptoms from baseline to each visit and end of therapy was analyzed and tested by Chi Square test. In this study all P values were reported based on two-sided tests and these statistical tests were interpreted at the 5% level of significance. Symptom gradation was analyzed by chi square test. Qualitative variables were presented as counts and percentages.

4. RESULTS

In the present study, 34 subjects were screened. Out of 34 subjects, 4 were dropped out of study as they lost to follow up. 30 subjects were considered evaluable cases at the end of the study.

4.1 Demographic Data

Out of 30 completed subjects, 25 were female subjects with a mean age of 45.15 ± 10.22 years. Out of 30 completed subjects, 05 were male subjects with a mean age of 50.10 ± 7.45 years. The details are presented in the following Table 3.

Table 3. Demographic details		
Parameters	**Female**	**Male**
No. of Cases	25	05
Mean	45.15	50.10
SD	10.22	7.45
Range	34 to 56 years	42 o 58 years

4.2 Efficacy Assessments

4.2.1 Assessment of Burning micturition: Number of subjects presenting assessment category based on grades (Represented as number of subjects as well as % population)*

Assessment of Symptoms (*Grades- 0 = None, 1= Mild, 2= Moderate and 3= Severe)

Out of 30 subjects 70% were experiencing Moderate burning micturition and 30% with severe burning micturition. After 30 days treatment with test drug there were 26.66% subjects reported no burning micturition and 73.33% with mild burning micturition. Till the end of study period 83.33% subjects completely recovered from burning micturition and 16.66% still experienced with mild burning micturition. Results were demonstrated in Table 4.

Table 4. Assessment of burning micturition				
Score	**Baseline**	**Day 30**	**Day 60**	**Day 90**
0	0	8 (26.66%)	20 (66.66%)	25 (83.33 %)
1	0	22 (73.33%)	10 (33.33%)	5 (16.66%)
2	21 (70 %)	0	0	0
3	9 (30 %)	0	0	0

Value represents No. of subjects representing the assessment score. Chi Square test was used to assess the values between baseline, day 30, 60 and end of the study P<0.0001 Significant.

4.2.2 Assessment of Intermittent urination: Number of subjects presenting assessment category based on grades (Represented as number of subjects as well as % population)*

Assessment of Symptoms (*Grades- 0 = None, 5= Mild, 7= Moderate and 9= Severe)

Out of 30 subjects 66.66 % were experiencing Moderate Intermittent urination and 33.33% with severe intermittent urination. After 30 days treatment with test drug there were 40% subjects reported no intermittent urination and 60% with mild intermittent urination. Till the end of study period 93.33% subjects completely recovered from intermittent urination and 6.66% still experienced with mild intermittent urination. Results were demonstrated in Table 5.

Table 5. Assessment of Intermittent urination				
Score	**Baseline**	**Day 30**	**Day 60**	**Day 90**
0	0	12 (40.00 %)	20 (66.66 %)	28 (93.33 %)
1	0	18 (60.00 %)	10 (33.33 %)	2 (6.66 %)
2	20 (66.66 %)	0	0	0
3	10 (33.33 %)	0	0	0

Value represents No. of subjects representing the assessment score. Chi Square test was used to assess the values between baseline, day 30 and end of the study P<0.0001 Significant.

4.2.3 Assessment of Pain during urination: Number of subjects presenting assessment category based on grades (Represented as number of subjects as well as % population)*

Assessment of Symptoms (*Grades- 0 = None, 5= Mild, 7= Moderate and 9= Severe)

Out of 30 subjects 66.66 % were experiencing Moderate pain during urination and 33.33% with severe pain during urination. After 30 days treatment with test drug there were 33.33% subjects reported no pain during urination and 33.33% with mild pain during urination. Till the end of study period 86.66% subjects completely recovered from pain during urination 13.33% still experienced with mild pain during urination. Results were demonstrated in Table 6.

Table 6. Assessment of pain during urination				
Score	**Baseline**	**Day 30**	**Day 60**	**Day 90**
0	0	10 (33.33 %)	20 (66.66 %)	26 (86.66 %)
1	0	10 (33.33 %)	10 (33.33 %)	4 (13.33 %)
2	20 (66.66 %)	10 (33.33 %)	0	0
3	10 (33.33 %)	0	0	0

Value represents No. of subjects representing the assessment score. Chi Square test was used to assess the values between baseline, day 30 and end of the study P<0.0001 Significant.

4.2.4 Assessment of global evaluation for overall improvement by investigator

In Test Group N=30, 25 (83.33 %) subjects reported very much overall improvement and 05 (16.66%) subjects reported much overall improvement at the end of the study as per investigator assessment.

4.2.5 Global assessment for overall improvement by subject

In Test Group N=30 , 21 (70.00%) subjects reported very much overall improvement and 08 (26.66%) subjects reported much overall improvement at the end of the study as per subject assessment. 01 (3.33%) subjects reported minimally overall improvement at the end of the study as per subject assessment.

4.2.6 Tolerability of study drug by physician

As per physician, In Test Group N=30, physician reported excellent Tolerability of study drugs for 25 (83.33%) and physician reported Good Tolerability of study drugsfor5 (16.66%) at the end of the study as per physician assessment.

4.2.7 Tolerability of study drug by subjects

As per subjects In Test Group N=30 , 20 (66.66%) subjects reported excellent Tolerability of study drugs and 10 (33.33%) subjects reported Good Tolerability of study drugs at the end of the study as per physician assessment.

5. DISCUSSION

Urinary tract infections (UTIs) are among the most prevalent microbial diseases and their financial burden on society is substantial. These accounted for nearly seven million office visits and one million emergency department visits, resulting in hospitalizations. UTI states the existence of bacterial pathogens within the urinary tract. Broadly categorized by the location of infection, which can be further classified to be asymptomatic or symptomatic, known to have wide-range of symptoms fluctuating from mild irritative annulling to bacteremia, sepsis. UTIs that occur in a normal genitourinary tract with no prior instrumentation are termed 'uncomplicated' (uUTI), whereas infections that are associated with structural or functional abnormalities, including instrumentation such as indwelling urethral catheters, and are frequently asymptomatic are termed 'complicated' (cUTI). The main causative pathogen involved in recurrent UTI in women is *Escherichia coli*, which accounts for about 80% of all episodes. Other significant pathogens include *Staphylococcus saprophyticus*, *Klebsiella pneumoniae* and *Proteus mirabilis*; each causes about 4% of all episodes of acute cystitis. Diagnosis and management can be done based on symptoms alone without further laboratory confirmation. In complicated or questionable cases, urinalysis is done to confirm the diagnosis and to detect the presence of urinary nitrites, red blood cells (RBCs), white blood cells (leukocytes), leukocyte esterase or bacteria. Recently, there has been greater emphasis on the search for herbal preparations that can be a help in the management of urinary disorders. In the Indian medical literature, many drugs have been advocated for this indication. CV-HFU01 is a well-balanced, multi-ingredient formula with proven value in a variety of urinary disorders. It is a natural and effective alkalizer, not only relieves burning micturition, but also soothes inflamed urinary mucosa. It restores normal urinary pH and normalizes the frequency of micturition. It is effective for long-term prophylaxis of UTI. Some of the pharmacological actions which are responsible for the activity of the formulation are as follows-

5.1 Shodhit Guggul (Commiphora mukul)

Guggul is one of the very ancient Ayurvedic drugs, having been first described in Atharva Veda (2000 B.C). According to Sushrut Samhita, guggul is, when taken orally, curative of obesity, liver dysfunction, internal tumors, malignant sores and ulcers, urinary complaints, fistula-in-ano, intestinal worms, leucoderma, sinus, edema and sudden paralytic seizure. The hydroxylated metabolites, cis- and trans-7βhydroxyl-4,17(20)-pregnadien-3,16-dione and 6β,11αdihydroxyl-4,17(20)-pregnadien-3,16-dione, have antibacterial activity, whereas the 11α-hydroxylated metabolite has free radical-scavenging activity.[25-26]

5.2 Gokhru Panchang (Tribulus terrestris)

It belongs to the family Zygophyllaceae. The common name is Kharkhasak, Gokhru. It is diuretic, anti-cancer, anthelmintic, antibac-terial and aphrodisiac. It contains active constituents for therapeutic-tic values such as gitogenin, chlorogenin, tribuloside, kaempferol, rhamnose, saponins, stigmasterol, β-sitosterol, neo-tigogenin, heco-genin, tribulosin, neo heco genin glucoside and cinnamic amide. Antimicrobial activity of organic and aqueous extracts from fruits, leaves and roots of Tribulus terrestris L., an Iraqi medicinal plant used as urinary anti-infective in folk medicine, was examined against 11 species of pathogenic and non-pathogenic microorganisms: Staphylococcus aureus, Bacillus subtilis, Bacillus cereus, Corynebacterium diphtheriae, Escherichia coli, Proteus vulgaris, Serratia marcescens, Salmonella typhimurium, Klebsiella pneumonia, Pseudomonas aeruginosa and Candida albicans. [27-28]

5.3 Sounth (Zingiber officinale)

Ginger (Zingiber) is a perennial herb belongs to Zingiberaceae family, having strong antibacterial activity and to some extent antifungal properties. It inhibits the growth of Escherichia coli, Proteus sp, Staphylococci, Streptococci and Salmonella. Literature reveals that the methanolic extract of Zingiber officinale exhibited considerable antibacterial activity against E. coli from various UTI. The antimicrobial activity of ginger may be attributed to the fact that it contains antimicrobial substances such as zingiberol, zingiberene and bisabolene. [29-30]

5.4 Marich (Piper nigrum)

Many literature reviews have shown the antimicrobial potency of black pepper. Extract of black pepper using solvent *viz.* carbon tetrachloride, benzene, ethyl acetate, acetone, methanol, ethanol, and distilled water were tested against gram-positive and gram-negative bacteria *viz. Staphylococcus albus, S. typhi, E. coli, B. megaterium, P. aeruginosa* and one fungus, *Pseudomonas aeruginosa*. Against

different bacteria, the strongest antibacterial and antifungal activity was shown at the concentration of 40µg/disc. All 20 strains of *K. pneumoniae* were isolated from the urine culture of a hospitalized patient suffering from urinary tract infection (UTI) and alcoholic extract of *P. nigrum* was tested against it, which showed good activity against antibiotic resistant *Klebsiella pneumonia* with MIC and MBC values at 0.62 mg/ml. [531-32]

5.5 Pippali (Piper longum)

Long pepper exhibits antibacterial activity; its isolates are active against Gram positive bacteria and moderately active against Gram negative bacteria. Each isolate is highly active against at least one particular species of bacteria: piperlonguminine againstBacillus subtilis and piperine against Staphylococcus aureus. [33-34]

5.6 Harad (Terminalia chebula)

It offers antibacterial, antiviral, and antifungal effects. The etha-nolic extract of myrobalan fruit has been found effective against both gram-positive and gram-negative bacteria such as Salmonella typhi, Staphylococcus epidermidis, Staphylococcus aureus, Bacillus subtilis, and Pseudomonas aeruginosa. The ethanolic extract of *Terminalia chebula* was found to be more potent against urinary tract associated pathogenic *Proteus vulgaris* strains. The extract of *Terminalia chebula* at the concentration of 100% has antibacterial activity on the tested microorganisms from high to low *Escherichia coli, Shigella flexneri* and *Pseudomonas aeruginosa* respectively. [35-36]

5.7 Baheda (Terminalia bellirica)

Methanol and aqueous extracts of the dried pericarp of T. bellirica fruits contained non-toxic polar antibacterial compounds with high thermal stability, which inhibited the growth of drug-resistant wild strains of S. aureus, Acinetobacter spp., P. aeruginosa and E. coli. The extraction of T. bellerica fruit in boiling water (heating under reflux) was found to be the most effective in terms of yield, antimicrobial potency and antioxidant potential of the extract. The antibacterial extracts possessed high antioxidant activity that correlated with the total phenolic content of the extracts. [37]

5.8 Awala (Emblica officinalis)

Aqueous extracts of the fruit pulp of E. officinalis were evaluated for antimicrobial activity against gram-positive bacteria Staphylococcus aureus, gram-negative bacteria Escherichia coli and fungal strains of Candida species by using agar cup plate method. The extracts showed a different degree of activity against pathogenic microbes. Aqueous infusion and decoction of E. officinalis exhibited potent antibacterial activity against *E. coli, Klebsiella pneumoniae, K. ozaenae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, S. paratyphi A, S. paratyphi B* and *Serratia marcescens*. [38-39]

5.9 Nagarmotha (Cyperus rotundus)

Cyperus rotundus contained flavonoids, tannins, glycosides, furochromones, monoterpenes, sesquiterpenes, sitosterol, alkaloids saponins, terpenoids, essential oils, starch, carbohydrates, protein, separated amino acids and many other secondary metabolites. It exerted antiparasitic, insecticidal, repellent, antibacterial, antioxidant, anticancer, central nervous, neuroprotective, anti-inflammatory activities. It was found to be active against E. coli, K. pneumoniae, P. vulgaris and Staphylococcus aureus. The findings of the study inferred broad-spectrum antibacterial activity of C. rotundus extract against UTI isolates. The MIC of the ethanolic extract of C. rotundus against UTI isolates ranged between 2.5 and 10mg/mL. [40-41]

5.10 Punarnava (Boerhaavia diffusa)

In vitro study to establish the antimicrobial effect of leaves of Punarnava (Boerhaviadiffusa) and Punarnavasava formulation on pathogens (Klebsiella species, Pseudomonas species, Enterococcus species, Escherichia coli and Proteus species) causing Urinary Tract Infection. Pharmacological research conducted on Punarnava confirmed that it contains punarnava side. It has an extensive range of properties like diuretic anti-inflammatory, antibacterial and anthelmintic. The purified glycoprotein from B. diffusa exhibited antibacterial effects against bacteriophages nucleic acid. [-42-43]

5.11 Varun Chhal (Crataeva nurvala)

The skin, roots and leaves of varuna have great medicinal value. The plant is used internally as well as externally. It is applied externally on wounds, reduces inflammation, loss of appetite, abdominal pain in liver disorders, worm infestation, dysuria, pain in urinary tract, urinary tract infection, fever and in general weakness. Chloroform extract of stem bark of Varun (Crataeva nurvala) is found to be effective against both gram positive (B. cereus) and gram negative (E. coli) mediated urinary tract infection and prostatitis at minimum inhibitory concentration. Varun bark decoction along with Apamarg, Punarnava, Yavakshara, Gokhuraand Yastimadhu given in Diabetes, Painful bladder, Urolithiasis and any other urinary tract diseases. [44-45]

6. CONCLUSION

In the study, subjects undergoing the treatment duration of 90 days but in first 30 days 80% subjects presented complete recovery from all the symptoms related to UTI. Also the adverse events for the 80% subjects in last 60 days were almost negligible who responded the CV-HFU01 very well. Thus CV-HFU01 was safe and effective alternative in the management of recurrent UTI. The product CV-HFU01 holds promising potential in urinary system disorders. The future scope of the study is to evaluate long term study as a therapeutic intervention in complicated urinary tract infections as well as adjuvant in active UTI with antibiotics.

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8. AUTHORS CONTRIBUTION STATEMENT

Ms. Gayatri Ganu and Dr. Tanuja Panchabhai conceptualized and gathered the data with regard to this work. Dr. Veena Deo and Mr. Bhushan Shrikhande conceptualized product, analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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