CASE STUDY

Effect of Berberine Supplement in Iraqi Sample of Type 2 Diabetic Patients with Recurrent Urinary Tract Infections

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ABSTRACT

In recent years, *in vitro* and *in vivo* research has shown that the Chinese traditional herb berberine, commonly used to treat bacterial diarrhea, decreases blood glucose levels. Berberine's efficacy and safety in treating patients with recurrent urinary tract infections (UTIs) in type 2 diabetes were assessed in this randomized, single-blind controlled study. Metformin was given to 60 persons with documented type 2 diabetes and UTIs for 12 weeks. According to the study, group A (Control group) received metformin (0.5 g t.i.d.) and group B received a mixture of berberine (0.5 g b.i.d.) and metformin (0.5 g t.i.d.) with a 24 weeks follow-up period. After 12 weeks of treatment, the medicinal plant berberine reduces the recurrence of UTIs in patients with type 2 diabetes mellitus (T2DM) by significantly lowering pyuria (WBCs/HPF), bacteriuria (>10^5 CFU/mL), and hematuria (RBCs/HPF) in patients compared to pre-treatment values and the control group. Fasting plasma glucose levels in both groups decreased significantly after 12 weeks of treatment for type 2 diabetes, relative to pre-treatment values and between groups. The berberine group saw a statistically significant decrease in urea, but not in creatinine or uric acid.

In conclusion, this randomized study indicates that using berberine supplements to treat, prevent, and reduce recurring urinary tract infections in type 2 diabetes.

Keywords: Metformin, Urinary tract infections (UTI), Berberine, Type 2 diabetes, Uropathogens

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INTRODUCTION

People with diabetes mellitus (DM) have a variety of illnesses that cause their blood sugar levels to stay high for a long time. People with DM also have metabolic problems with how their bodies process carbohydrates, fats, and proteins. Either way, these problems can cause long-term damage, malfunction, and failure of different parts of their bodies.[1]

The urinary system is the most prevalent location of infection in people with type 2 diabetes (T2D). Furthermore to inadequate metabolic regulation of diabetes, various impairments in the immune system`, higher urine glucose concentrations can facilitate the development of pathogenic bacteria and insufficient emptying of the bladder due to autonomic neuropathy decreasing physical bacterial clearance *via* micturition, promoting bacterial development can all lead to the pathogenesis of diabetic patients with urinary tract infections (UTI).[2]

Infections of the urinary tract refer to the presence of urinary tract microorganisms, including bladder, prostate, collection system, or kidneys. UTI is a urothelial inflammatory response to bacteria, an invasion commonly associated with bacteriuria and pyuria, and UTIs caused by microorganisms, which enter the urethra and bladder, causing inflammation and infection.[3]

These bacteria can also migrate and invade the kidneys via the ureters. UTI are most frequently caused by either bacteria caused by a variety of pathogens, but most frequently by' *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis,* and *Staphylococcus saprophyticus'* or sometimes by fungi and viruses. High rates of recurrence and increasing resistance of uropathogens to antimicrobials threaten a significant increase in the economic burden of these infections.[4]

When the amount of causative agents in a urine culture or urine analysis exceeds 100,000 CFU/mL, the odds of a UTI

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increase dramatically. When a UTI is suspected, a midstream urine specimen should be checked for the presence of leukocytes, as pyuria is present in almost all UTI cases. Pyuria can be discovered via a microscopic inspection (defined as 10 leukocytes/mm^3) or a dipstick leukocyte esterase test (75–96% sensitivity and 94–98% specificity compared to microscopic examination, which is the gold standard).[5]

Recurrent UTIs (rUTIs) are "described as having more than two infections in 6 months or three infections in 12 months, with at least two weeks of complete resolution". A relapse may cause these due to inadequate management (persistence) or re-infection (new source) caused by the same pathogen. There are many risk factors for rUTIs, including immune system deficiency and virulence factors in the body.[6]

Some foods with an anti-adhering action that inhibits *E. coli* may also be useful in preventing recurrent UTIs. Medicinal plants have been utilized to treat and prevent ailments since ancient times. Due to their low side effects, low cost, easy accessibility, lack of bacterial resistance, and tolerance for UTI patients, medicinal herbs have gained widespread appeal and trustworthiness. Phytochemical substances work as nutraceuticals and immunomodulators, boosting the body's oxidant status or providing antioxidant chemicals, inhibiting microbe attachment, and halting microorganism development.[5,7]

Berberine is a popular OTC medicine in China, used to treat gastrointestinal illnesses. Chemically, berberine and other isoquinoline alkaloids, such as thiazolidinediones and acarbose, are very different from other hypoglycemic drugs like sulphonamides, biguanides, and acarbose. A new class of anti-diabetic drugs could be created with the efficacy and safety of berberine verified.[8]

Berberine supplementation in T2D patients is being examined for its antibacterial in the treatment and prevention of recurrent urinary tract infections in this randomized study.

SUBJECTS AND METHODS

The National Diabetes Center (NDC), Mustansyriah University conducted this randomized, single-blind, controlled study from September 2020 to November 2021. The Scientific and Ethics Committee of the College of Pharmacy, Mustansiriayah University, as well as the Scientific Committee of the National Diabetes Center, examined and approved the protocol. All participants have agreed to the research goal, and the consent form has been signed. Only those who signed informed consent forms and met the following criteria were considered for participation.

The inclusion criteria include patients with T2D aged between (30–50) years according to American Diabetes Association criteria,[9] and patients presenting with urinary symptoms of UTI and a history of recurrent UTI (defined as more than two episodes in the last six months or three episodes in the last year).[10]

The exclusion criteria include; patients with known allergies or intolerances to berberine supplement ingredients were excluded. Pregnant or postmenopausal women, males with prostatic illness, and those who refuse to avoid probiotics and yogurt. A comorbid or physical ailment patients with febrile UTI or hematuria, severe hepatic/renal impairment, or kidney stones immunocompromised patients other than diabetics or those taking steroids or immunosuppressive medicines, prophylactic antibiotic use, and patients taking high CYP450 inducers or inhibitors.

A consultant endocrinologist in NDC oversaw all patients during the trial, who were all diagnosed with diabetes and recurrent UTI. Anti-diabetic and UTI medications will be used as usual (metformin 500 mg three-time daily and cefixime 400 mg once daily for seven days, respectively). In total, 60 patients of both sexes were treated for a total of 12 weeks, and the completion of follow-up was scheduled for 24 weeks after the treatment began started and was scheduled at 12, 16, 20, and 24 weeks. In order to continue treatment, those who had been given berberine 500 mg capsule (Amazing nutrition; USA) were given a one-week deadline to return for the second session.

At the six-weeks mark, any side effects were documented, medication adherence was assessed, and berberine capsules were given out. Visit four took place six weeks after the last one, and this time, all of the lab measurements were taken. Subjects were instructed to keep as close to the scheduled time of their visits as they reasonably could. For groups, A (control group) and B (berberine groups), some participants (3 and 4, respectively) did not complete this study for unexplored reasons.

Group B, with 26 participants, compared berberine and metformin to metformin alone as a control group (group A, with 27 participants). Patients were reassessed 12 weeks following their initial evaluation. Creatinine, urea, uric acid, and fasting blood glucose were all tested (Figure 1-4). Using the student t-test and chi-square test (χ^2-test), the researchers determined whether or not lower urinary tract symptoms were associated with pyuria (WBCs/HPF), hematuria (RBCs/HPF), and bacteriuria (>100,000 CFU/mL).

A glucose oxidase technique (Biolabo Company, France) was used to determine fasting blood glucose creatinine concentrations were determined by enzymatic assays (Human, Germany), and urea and uric acid were determined by an assay kit produced by Biolabo Company, France.

General urine examination (GUE) was performed microscopically to detect pyuria (WBCs/high power field), hematuria (RBCs/high power field), and bacteriuria (number of cells/high power field). A urinary tract infection was assumed when bacteriuria over 100,000 CFU/ml and lower urinary symptoms were present.

Pyuria accompanied by a high level of bacteriuria (>10^5 CFU/mL) was considered an indication of a UTI and expressed as a percentage of infected patients. 'Sterile' pyuria is "pyuria without noticeable bacteriuria." urine was centrifuged 5 minutes at 400 g for 10 mL urine to analyze microscopically, Pyuria is defined as ≥5 WBCs per high-power (HPF) field in

Table 1: Baseline characteristics for control and berberine groups in T2D patients with recurrent UTI.

Baseline characteristics no		*Control*		*Berberine*		*p-value*
		%	*No*	*%*		
Age (years)	30–39	10	37.0	7	26.9	N.S
	40–49	14	51.9	15	57.7	
	50–59	3	11.1	4	15.4	
	Means ± SD	42.7 ± 6.1		43.4 ± 5.4		N.S
Gender	Male	14	51.9	11	42.3	N.S
	Female	13	48.1	15	57.7	
Number of UTI during last 24weeks	2	15	55.6	17	65.4	N.S
	3	12	44.4	9	34.6	
Duration of DM	<1year	14	51.9	12	46.2	N.S
	1–4	11	40.7	14	53.8	
	=>5years	2	7.4	-	-	
Marital status	Single	2	7.4	2	7.4	N.S
	Married	25	92.6	25	92.6	
Education	Read and Write	5	18.5	5	18.5	N.S
	Primary	4	14.8	4	15.4	
	Secondary	8	29.6	5	19.2	
	College	10	37.0	12	46.2	
Income(US $)	<500US$	8	29.6	12	46.2	N.S
	500–	14	51.9	12	46.2	
	=>750 US$	5	18.5	2	7.7	
	Mean ± SD	516.7 ± 213.5		428.8 ± 182.3		

N.S represent no significant difference between two groups regarding all baseline variables between percentages using Pearson Chi-square test (χ2-test) at 0.05 level

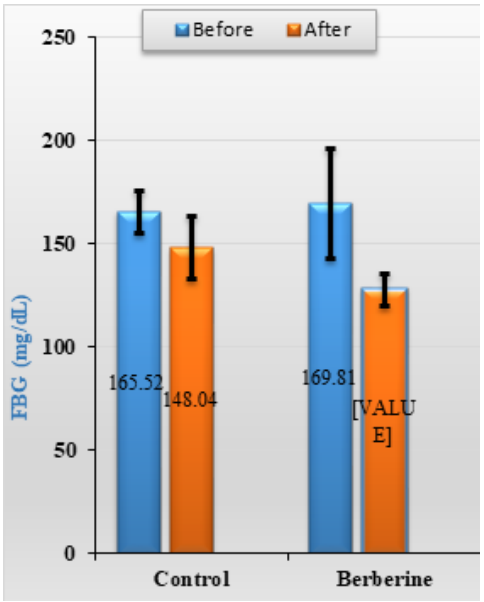

Figure (1): Effect of berberine groups on Fasting plasma glucose serum level after 12 weeks

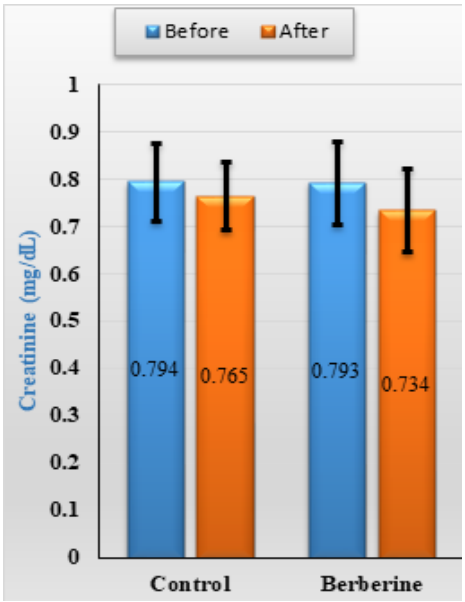

Figure (2): Effect of berberine groups on Creatinine level after 12 weeks of treatment.

Data expressed as mean < SD; * represent significant difference, ($p<0.05$) comparing with control group according to student t-test test. $p< 0.05$ (*$p< 0.05$, **$p< 0.01$, ***$p< 0.001$)

Table 2: Berberine effect on glycemic and renal function test groups in type 2 diabetic patients with recurrent UTI.

	Control group		*Berberine*	
	Baseline	*Endpoint (After 12 weeks)*	*Baseline*	*Endpoint (After 12 weeks)*
FBG mg/dL	165.52 ± 15.16	148.04 ± 10.40**	169.81 ± 26.60	127.77 ± 7.99**ab
Creatinine mg/dL	0.794 ± 0.083	0.765 ± 0.072*	0.793 ± 0.087	0.734 ± 0.074**
Urea mg/dL	27.14 ± 4.21	26.82 ± 4.29	28.01 ± 5.00	23.62 ± 3.31**a
Uric acid mg/dL	3.93 ± 0.59	3.57 ± 0.54*	4.15 ± 0.80	3.43 ± 0.38**

Data were presented as Mean ± SD.
* represent significant difference, ($p<0.05$) between pre and post-treatment group, within the same group using paired t-test.
** represent highly significant difference ($p\leq0.01$) comparing pre and post-treatment within the same group using paired t-test.
a represent significant difference, ($p<0.05$) comparing with control group according to student t-test test.
ab represent highly significant difference ($p\leq0.01$) comparing with control group to student t-test test.
FBG, Fasting blood glucose.

Table 3: Effect of Berberine in pyuria and hematuria groups in type 2 diabetic patients with recurrent UTI.

	Control group		*Berberine*	
	Baseline	*After 12 weeks*	*Baseline*	*After 12 weeks*
Pyuria changes (WBCs/HPF)	17.15 ± 5.40	16.26 ± 5.56	17.96 ± 4.81	5.92 ± 5.34 **ab
Hematuria changes (RBCs/HPF)	4.81 ± 2.00	4.30 ± 2.02	4.14 ± 1.21	2.12 ± 1.61**ab

Data were presented as Mean ± SD.
**represent highly significant difference ($p\leq0.01$) comparing pre and post-treatment, within the same group.
ab represent highly significant difference ($p\leq0.01$) comparing with control group to student t-test.
WBCs/HPF represent white blood cells per high-power field.

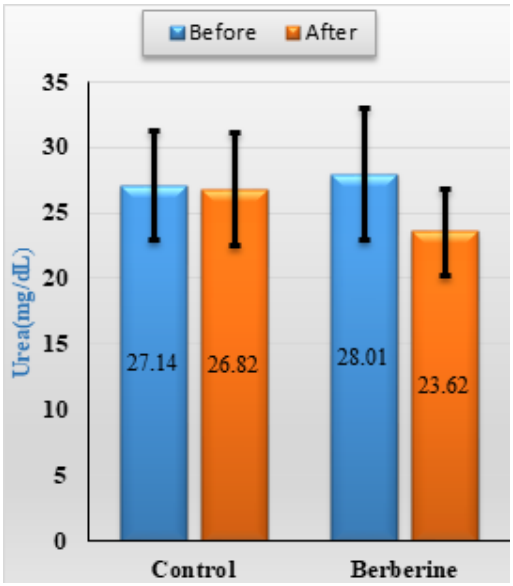

Figure 3: Effect of berberin groups on Urea serum level after 12 weeks of treatment

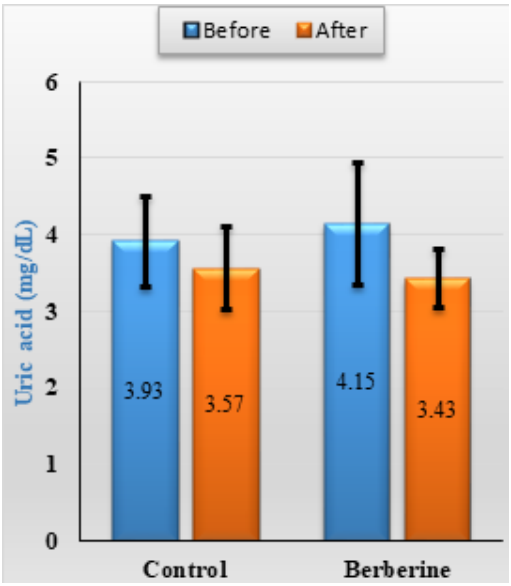

Figure 4: Effect of berberine groups on Uric acid serum level after 12 weeks of treatment.

Data expressed as mean < SD; * represent significant difference, ($p<0.05$) comparing with control group according to student t-test test.

centrifuged urine. Hematuria is defined as "red blood cells in the urine induced by an illness".[11]

Statistical Analysis

The SPSS-27 statistical software was used for data analysis (Statistical Packages for Social Sciences- version 27). The data were summarized using frequency, percentage, mean, and standard deviation as the primary metric for understanding the data. students t-test for differences between two independent means or paired t-test for differences between paired observations were used to determine the significance of the differences in the means (quantitative data) (or two dependent means). The Pearson chi-square test (χ^2-test) was used to determine the significance of the percentage differences (qualitative data). A statistically significant p-value of less than 0.05 was taken into consideration.

RESULTS

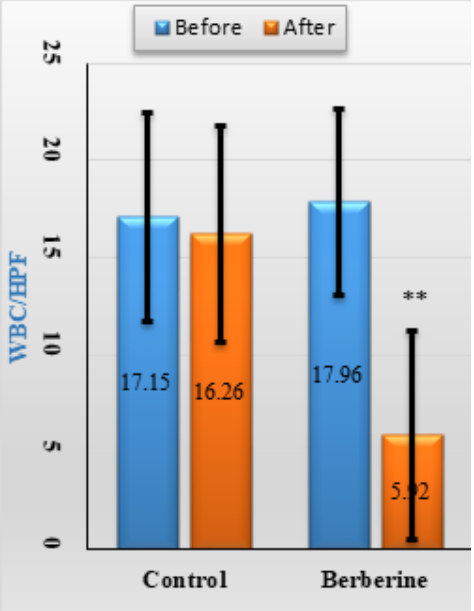

Figure 5: Effect of berberine groups on urine

RBCs/HPF represent red blood cells per high-power field

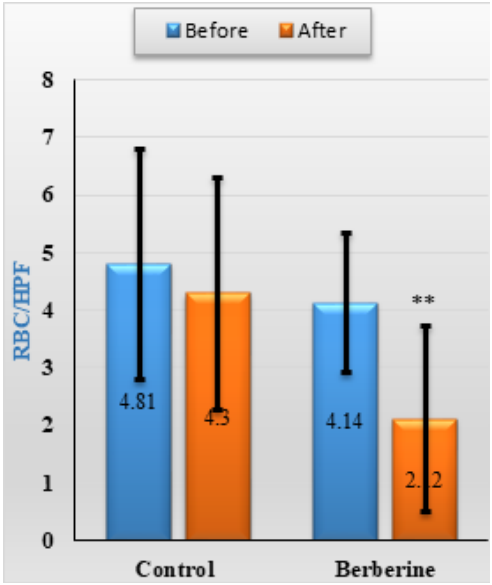

Figure 6: Effect of berberine groups on urine

Hematuriam, pyuria (WBC/HPF) at baseline and after (RBC/HPF) at baseline and after 12 weeks of treatment. Data expressed as mean < SD; * represent significant difference, ($p < 0.05$) comparing with control group according to student t-test test. $p < 0.05$ (*p< 0.05, **p< 0.01, ***p< 0.001)

Table 4: Effect of berberine in bacteriuria groups in type 2 diabetic patients with recurrent UTI.

Bacteriuria changes ((>105 CFU/mL= infected)) no		*Control*		*Berberine*	
		%	*No*	*%*	
Bacterial infection bacteriuria changes ((>105 CFU/mL: i.e. infected)) at Baseline	Bacteria found	27	100	26	100
	No	-	-	-	-
Bacterial infection bacteriuria changes ((>105 CFU/mL: i.e. infected)) after 12 weeks	Bacteria found	21	77.8	2	7.7*
	No	6	22.2	24	92.3

*Significant difference between percentages using Pearson chi-square test (χ2-test) at 0.05 level.
CFU, colony-forming unit

Table 5: Effect of berberine groups in type 2 diabetic patients on recurrence of urinary tract infection after 24 weeks follow up:

Recurrence of UTI No		*Control*		*Berberine*	
		%	*No*	*%*	
After 12 weeks	Infection	21	77.8	2	7.7
	No	6	22.2	24	92.3*
16 weeks	Infection	7	25.9	-	-
	No	20	74.1	26	100
20 weeks	Infection	13	48.1	1	3.8
	No	14	51.9	25	96.2*
24 weeks	Infection	9	33.3	1	3.8
	No	18	66.7	25	96.2*

*Significant difference between percentages using Pearson Chi-square test (χ2-test) at 0.05 level.

In this study, 60 diabetic patients with recurrent UTI were included and randomly assigned to the control group (group A, $n = 27$). Berberine group with metformin (group B, $n = 26$) and metformin alone; as three patients of the control group and four patients of the berberine group withdrew from this study for unexplored reasons before week 12. Thus, 53 participants were eligible for the final analysis.

For this investigation, demographic and baseline data were gathered (Table 1). Between groups, there were no statistically significant differences. Of the 53 patients included in the study, 25 were men, and 28 were women. The A group was formed by 14 men and 13 women, with a mean age of (43.7 ± 6.1) years, the B group by 11 men, and 15 women with a mean age of (43.4 ± 5.4) years.

When comparing berberine to control groups using a student t-test, we found a statistically significant ($p>0.05$) reduction in fasting plasma glucose levels; the BBR group had a non-significant reduction in creatinine and uric acid levels and a significant decrease in urea concentrations (Table 2).

The urinalysis results have shown a significant decrease in pyuria (WBCs/HPF), hematuria alterations (RBCs/HPF) and bacteriuria (exceeded 100,000 CFU/mL considered infected) after treatment with berberine for 12 weeks compared to control (Tables 3 and 4) and (Figures 5 and 6).

The number of recurrent UTI episodes recorded through planned at 12, 16, 20, and 24 weeks is shown in Table 5. In detail, during the trial, 7.7, 3.8, and 3.8% of the berberine group experienced UTI episodes at 12, 20, and 24 weeks, respectively, compared to 77.8, 48.1, and 33.7% of the control group at 12, 20, and 24 weeks, respectively.

DISCUSSION

Diabetes mellitus (DM) is a long-term condition that leads to various irregularities and metabolic problems in those with it. DM has been linked to an increased incidence of infections, including UTIs. The frequency and severity of UTIs are both higher in those with DM.[12,13]

There is a significant rate of UTI among people with diabetes. Several investigations have proven the link between uncontrolled DM and increased UTI risk. Females were more likely than males to contract the disease.[14]

DM increases the risk of recurrent UTI. A United States database analysis found that recurrent UTI occurs in 1.6% of T2D and 0.6% of non-DM individuals. DM also raises the risk of acute pyelonephritis and severe urosepsis, such as emphysematous pyelonephritis (EPN) or renal abscess. In a large case-control study, premenopausal women with DM had 4.1 times the risk of UTI and acute pyelonephritis. Another study found that DM patients are 5.9–24.1 times more likely than non-DM patients to be hospitalized for UTI and acute pyelonephritis.[15] Bacteria may proliferate faster in DM urine; there was a 21% increase in UTI per 1% increase in recent HbA1c. Hyperglycemia in DM patients impairs immunological responses, allowing infections to invade and proliferate. Hyperglycemia reduced IL-2, 6, and 10 productions, also impaired leukocyte recruitment, granulocyte, and natural killer cell activity.[16]

Berberine has been demonstrated in numerous studies to have anti-diabetic effects. Insulin sensitivity, activation of the AMPK pathway, induction of glucagon-like protein-1 secretion from the gut, stimulation of glycolytic processes in peripheral tissues, inhibition of gluconeogenesis, an increase in glucose transporters in cells, and a decrease in -glucosidase activity are just a few of the possible mechanisms underlying this effect.[17]

The current investigation found that berberine had a significant effect on FPG serum levels, in accordance with the conclusions of this study of Homeira Rashidi, *et al.,* 2018,[18] LadanTahmaseb, *et al*., 2019,[19] and Rasool Soltani, *et al*., 2021, discovered that patients with T2DM, had significant improvements than the control group, which is consistent with our findings.[20]

Berberine has a protective impact on the kidneys, and that it is also through administration provided morphological and functional protection. Apoptosis and oxidative stress were avoided in renal injury due to Ischemia-reperfusion (I/R) by administering berberine. Degradation of oxidative and mitochondrial stress pathways may account for most of the protective benefits according to possible mechanisms.[21] We found significant reductions in blood creatinine and urea concentrations after 12 weeks of berberine administration compared to baseline and significant reductions in serum urea concentrations compared to the control group.[22] These results are in line with those of the current study and of Rashidi H *et al*., 2018.[23]

The most common UTI ailment is cystitis "Infectional bacteria of the bladder that causes symptoms such as burning, urine frequency (including nocturia), and urgency". *E. coli* is by far the most prevalent uropathogenic found in the urine of people with diabetes, followed closely by *K. pneumonia*. Antibiotic resistance patterns are quite varied; however, ampicillin, Trimethoprim-sulfamethoxazole, and cefotaxime resistance were found in the majority of microorganisms. Antibiotic prescribing data showed that cephalosporin's and penicillin were the two most regularly prescribed classes of drugs.[24]

Acute and recurrent UTIs are commonly treated with antibiotics, but this can lead to dysbiosis of the normal vaginal and intestinal flora and antibiotic resistance because of the high mutation and horizontal gene transfer capabilities of different pathogens. Uropathogens alter their appearance, infiltrate uroepithelial cells, and build biofilms to survive and cause recurrent infections.[25]

Additionally, uropathogens persist in the bladder in a number of ways under conditions of starvation and immune responses. Uropathogens undergo morphological changes, infiltrate uroepithelial cells, and form biofilms to remain and cause repeated infections. Extracellular DNA, exopolysaccharides, pili, flagella, and other sticky threads provide a safe haven for bacteria resistant to antibiotics, immunological reactions, and other pressures. As a result, it is past time to investigate alternative techniques of preventing and treating UTIs.[26]

Medicinal herbs have achieved worldwide appeal and trustworthiness due to their low reported adverse effects, low cost, easy availability, lack of bacterial resistance, and tolerance towards UTI sufferers. According to WHO, medicinal plants are used by 80% of the world's population and 30% of pharmaceutical formulations. Phytochemical ingredients acted as nutraceuticals and immunomodulators, boosted body oxidant status or provided antioxidant compounds, prevented microbe attachment, halted microorganism proliferation or multiplication, and some may act as microbial. These different effects of medicinal plants are attributed to several phytochemical elements, including alkaloids, anthraquinones, flavonoids, and glycosides.[27]

For all the aforementioned reasons, berberine (a medicinal plant) is used in the present study to treat recurrent UTIs in

people with T2D. The reduction in pyuria (WBCs/HPF), hematuria (RBCs/HPF), and bacteriuria (>10^5 CFU/mL) in berberine groups of T2DM patients treated after 12 weeks was statistically significant (p>0.05) compared to control

Berberine chloride act as antimicrobial. Decreasing enzyme activity and modifying the surface structure of bacterial cell walls affects DNA duplication, RNA transcription, and protein synthesis in bacterial cells. For instance, Jin, *et al*. demonstrated that *in-vitr*o exposure to berberine of several bacterial generations (including *E. coli*) makes resistance development difficult due to a scarcity of viable and metabolically active clones.[28]

A. baumannii isolates were found to be inhibited by berberine by the mean inhibition zone around the berberine disks. Findings from this study show that berberine has antibacterial qualities that can help treat *A. baumannii* resistant to imipenem and ciprofloxacin. *A. baumannii* infections may be treated with berberine in the future [(29)].

Berberine can also affect PAP (pyelonephritis-associated pili) fimbriae uropathogenic *E. coli* (UPEC) production and expression. These odd fimbriae operate as adhesion virulence elements in UPEC kidney colonization. *In vitro* berberine pre-treatment reduced UPEC sticky and invasive abilities. Using an *in-vivo* model, we can explore the dynamics of infection and the impact of berberine pre-treatment and co-incubation, and berberine is an essential antibiotic that fights infections by inhibiting bacteria (such as *E. coli* and *Proteus* species) from adhering to the host cell, implying that it could be useful in treating UTI.[30]

The effects of the berberine on bacterial cystitis prevention and therapy in a rat model; Murat Tuken, *et al*., 2017, found that long-term (14 days) treatment with a herbal substance added to the drinking water cleared the urine of *E. coli*, but only partially.[31]

There are numerous clinical applications for berberine hydrochloride. It has also been widely used as a pharmaceutical source due to its low cost, little side effects, and widespread use, despite its mechanism of action being still unknown. Antibacterial, antiviral, anti-inflammatory, analgesic, anticancer, hypoglycemic, antilipidemic, antihypertensive, anti-arrhythmic, anti-heart failure, etc. are some of the uses of this ingredient. Treatment of gastroenteritis, bacterial diarrhea, gastrointestinal illness, conjunctivitis, and middle ear infection with this medication is commonplace.[32]

Even though there is no previous study on the effect of berberine therapy on recurrent UTI in T2D patients to interpret these findings, the reasons previously mentioned can explain the result found, which shows the number and percentage of UTIs episodes observed during the intervention and follow-up periods; in detail during the study period. Berberine group had 7.7, 3.8, 3.8% UTI episodes during the 12, 20, and 24 weeks follow-up periods, compared to the control group (92.6, 11.1, and 33.7%) at 12, 20 and 24 weeks follow-up periods. Berberine have less percentage of recurrency of UTI since it acts as an anti-diabetic drug in addition to its antimicrobial and anti-inflammatory action, as mentioned before.

However, no previous studies are testing the efficacy of extract of berberine on diabetic patients with recurrent UTI, to interpret these findings in the present study, which was a substantial decrease in pyuria, bacteriuria, and hematuria compared to the baseline and control groups and decrease the percentage of recurrent UTI through follow up period.

CONCLUSION

Recurrent UTIs among T2D can be treated, and prevented, and the incidence of recurrence reduced by using berberine supplements. When compared to the control group, berberine has a significant impact on FBG. It has been established that every treatment approach positively influences renal function.

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