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Research Article

Effect of Grape Seed Proanthocyanidins Supplement on the Incidence of Recurrent Urinary Tract Infections in a Sample of Iraqi Diabetic Patients

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Abstract

Background: Proanthocyanidin is often used to prevent urinary tract infections (UTIs) in susceptible *E. coli* strains. ***Objective***: To explore how grape seed proanthocyanidin extract (GSPE) affects type 2 diabetic patients (T2DM) with recurrent urinary tract infections (rUTIs). ***Method***: The efficacy of GSPE in the treatment of T2DM with rUTIs was assessed in this randomized, single-blind controlled study. Sixty adults with diagnosed T2DPs and urinary tract infections were randomly assigned to treatment for 12 weeks with metformin (0.5 g t.i.d.) in Group A (Control Group) and a combination of GSPE (300 mg q.d.) and metformin (0.5 g t.i.d.), Group B, with the end of follow-up being 24 weeks, according to the study. ***Results***: The medicinal plant GSPE reduces the recurrence of urinary tract infections in patients with T2DM after 12 weeks of treatment, compared with pre-treatment values and the control group. After 12 weeks of treatment for T2DM, fasting plasma glucose levels, creatinine, urea, and uric acid in both groups decreased non-significantly compared to control. There were fewer recurrent UTIs in the intervention group (77.8%), the control group (48.1%), and the GSPE (7.1%), compared to the control group (12.7%), the GSPE (7.1%), and the intervention group (33.7%) over the course of 24 weeks. ***Conclusions***: Utilizing GSPE to treat, prevent, and minimize recurrent urinary tract infections in T2DM will help them better grasp the benefits and hazards associated with the daily administration of an appropriate GSPE dose.

Keywords: Grape seed extract, Metformin, Proanthocyanidin, T2DM, UTIs, Uropathogenicity.

تأثير مكمل بروانثوسيانيدين بذور العنب على حدوث التهابات المسالك البولية المتكررة في عينة من مرضى السكري العراقيين

الخلاصة

الخلفية: غالبا ما يستخدم Proanthocyanidin للوقاية من التهابات المسالك البولية (UTIs) في سلالات الإشريكية القولونية الحساسة. **الهدف**: استكشاف كيفية تأثير مستخلص بذور العنب بروانثوسيانيدين (GSPE) على مرضى السكري من النوع 2 (T2DM) المصابين بالتهابات المسالك البولية المتكررة(rUTIs) . **الطريقة**: تم تقييم فعالية GSPE في علاج T2DM مع rUTIs في هذه الدراسة العشوائية أحادية التعمية. تم تعيين ستين بالغا يعانون من T2DM المشخصة والتهابات المسالك البولية بشكل عشوائي للعلاج لمدة 12 أسبوعا باستخدام الميتفورمين (0.5 جرام t.i.d.) المجموعة أ (المجموعة الضابطة) ومزيج من (300 GSPE ملغ q.d.) والميتفورمين (0.5 غرام t.i.d.)، المجموعة ب ، مع نهاية المتابعة 24 أسبوعا ، وفقا للدراسة. **النتائج**: يقلل النبات الطبي GSPE من تكرار التهابات المسالك البولية لدى مرضى السكري من النوع 2 بعد 12 أسبوعا من العلاج ، مقارنة بقيم ما قبل العلاج والمجموعة الضابطة. بعد 12 أسبوعا من العلاج ، انخفضت مستويات الجلوكوز في البلازما الصائمة والكرياتينين واليوريا وحمض اليوريك في كلتا المجموعتين بشكل غير ملحوظ مقارنة بالسيطرة. كان هناك عدد أقل من عدوى المسالك البولية المتكررة في مجموعة التدخل (77.8٪) ، والمجموعة الضابطة (48.1٪) ، و GSPE (7.1 ٪ (، مقارنة بالمجموعة الضابطة12.7 ٪ ، GSPE 7.1٪ ، ومجموعة التدخل 33.7٪على مدار 24 أسبوعا. **الأستنتاجات**: إن استخدام GSPE لعلاج ومنع وتقليل التهابات المسالك البولية المتكررة في T2DM سيساعدهم على فهم الفوائد والمخاطر المرتبطة بالإدارة اليومية لجرعة GSPE المناسبة بشكل أفضل.

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INTRODUCTION

A shortage of insulin, whether relative or absolute, is the root cause of diabetes mellitus, a long-term illness. Microvascular, macrovascular, neuropathic, nephropathic, and retinopathic problems have been linked to problems in carbohydrate, fat, and protein metabolism [1,2]. One of the most common endocrine disorders is diabetes mellitus, which affects more than 200 million people. DM is predicted to rise rapidly, and

in 2030, it will theoretically be the seventh leading cause of death. The Middle East and North Africa (MENA) region has the second-highest prevalence of diabetes (9.2 %). Between 2017 and 2045, the MENA region's diabetes population is predicted to double, to 629 million [3,4]. A 2018 age-adjusted survey by the World Health Organization (WHO) in Basrah, southern Iraq, revealed that approximately 5400 individuals aged 19 to 94 had diabetes. Inactivity, obesity, genetics, race/ethnicity, age, and family history are all associated with rising diabetes prevalence [5]. In diabetic patients, elevated sugar levels contribute to altered immune function, which is significantly correlated with various defects of the innate and adaptive immune systems, which can lead to an increased risk of having a urinary tract infection (UTI). Elevated levels of inflammatory markers are also associated with hyperglycemia, resulting in compromised immune functions such as reduced secretion of inflammatory cytokines, diminished activity of neutrophils and T cells, and impaired humoral immunity. Additionally, hyperglycemia hinders tissue recovery by altering growth factor secretion and collagenase levels, increasing the susceptibility to secondary bacterial infections. All of these advances make diabetic patients more likely to have infections such as UTIs, infections of the respiratory tract, and infections of the skin and soft tissue (SSTIs) [6]. A higher incidence of UTIs among diabetic women (75%), than diabetic men (25%), was observed in Iraq. Patients with diabetes who have frequent UTIs (68.8%) had a higher incidence of UTI complications, while non-diabetics had a lower prevalence (31.1%) [7,8]. Recurrent UTIs (rUTIs) are defined as two or more infections within six months or three infections within a year. The same bacteria caused relapses due to inadequate (persistence) treatment or reinfection (new source). Recurrent UTIs are caused by a lack of immunity and virulence factors in the body [9]. The most common causative organism for both complicated and uncomplicated UTIs is uropathogenic *Escherichia coli* (UPEC). Acute pyelonephritis, which is undetected and untreated, may lead to renal hypertension, renal scarring, and even renal failure [10]. Some foods in UTI have a preventive role, and they are effective in reducing the incidence of recurrent UTI. Since ancient times, medicinal plants have been used to cure and regulate different diseases, as they have beneficial effects. Even at the beginning of the 21st century, medicinal plants have gained growing popularity and reliability worldwide due to their less-recorded side effects, cost-effectiveness, easy accessibility, lack of bacterial resistance, and tolerance for UTI patients [11]. It was recorded that phytochemical constituents served as nutraceuticals and immunomodulators, boosting the oxidant status of the body or providing antioxidant compounds, preventing microbe attachment, as well as stopping the proliferation or multiplication of microorganisms [12]. Proanthocyanidins (PAC) are polymeric phenolic compounds found in the flowers, nuts, fruits, bark, and seeds of various plants and are naturally present as a safeguard against biotic and abiotic stressors in woody plants and herbaceous species. Their astringency protects the plants against pests and pathogens. Procyanidins are present exclusively in many popular foods, such as chocolate, apples, pears, grape seeds, blueberries, and cranberries [13]. Proanthocyanidin dimers are powerful antibacterial agents. It inhibited the viability of *Listeria monocytogenes*. In urinary and dental infections, they produce antibacterial anti-adhesive activity, inhibiting uropathogenic P-fimbriae-expressing multidrug-resistant *E. coli* strain adhesion. A-type proanthocyanidins reduced *Candida albicans* adhesion by inhibiting NFκ-B (NFκ-B p65 activation) and phosphorylation of unique signal intracellular kinases [14]. For the treatment and prevention of recurrent urinary tract infections, this randomized study aims to estimate the effectiveness of a grape seed proanthocyanidin extract supplement in type 2 diabetic patients.

METHODS

Study design and setting

From September 2020 to November 2021, the National Diabetes Center (NDC) at Mustansiriyah University conducted a randomized, single-blind, controlled study. This study had been planned to assess the effects of proanthocyanidin extract on T2DM patients who have recurrent urinary tract infections. During the study period, all patients were diagnosed and supervised by a consultant endocrinologist in NDC.

Patients' selection

The patients proceeded with their customary antidiabetic and UTI treatment (metformin 500 mg three-times daily and a fixed 400 mg once daily for 7 days) and dietary plan, receiving general guidance on their feeding and lifestyle adjustments; however, the instruction does not include calorie counting limitations.

Inclusion and exclusion criteria

Patients with type 2 diabetes aged 30–50 years, according to American Diabetes Association criteria [15], and patients with urinary symptoms of UTI and a history of recurrent UTI (defined as more than two incidents in the last six months or three episodes in the last year) were included in the study. Patients with known allergies or intolerances to grape seed are excluded from the study, according to the exclusion criteria. The study excluded men suffering from prostatic disease, women who are pregnant or postmenopausal, and individuals who refuse to give up probiotics and yogurt. A physical or comorbid condition Patients with a feverish UTI or hematuria, significant hepatic or renal impairment, or kidney stones should seek medical attention. Patients who are immunocompromised, whether they are not diabetic, are using steroids or immunosuppressive drugs, or are taking prophylactic antibiotics, should seek medical attention. During the trial, a consultant endocrinologist at NDC monitored all the patients, who were diagnosed with type 2 diabetes and recurrent UTIs.

Treatment and outcome analysis

Medications for diabetes and urinary tract infections (UTIs) will be used as usual (metformin 500 mg three

times daily and cefixime 400 mg once daily for seven days, respectively). A total of 60 patients of both sexes were treated for a total of 12 weeks, with follow-up scheduled at 12, 16, 20, and 24 weeks after therapy began. Those who had been given grape seed proanthocyanidin extract tablets 300 mg once daily were given a one-week deadline to return for the second session in order to continue therapy. Any side effects were reported, medication follow-up was examined, and grape seed extract (Proanthocyanidins) 300 mg tablets (Pureclinica, USA) were distributed at the six-week mark. Six weeks following the previous visit, the fourth one occurred, and this time all of the lab measurements were taken. Subjects were instructed to arrive as close to the scheduled time as feasible. Some individuals (3 and 2, respectively) in groups A (control group-metformin) and B (grape seed proanthocyanidin extract and metformin) did not finish the trial for unknown reasons. Group B has 28 individuals compared to control group A, which has 27 participants. Patients were re-evaluated 12 weeks after their original assessment. The levels of creatinine, urea, uric acid, and fasting blood glucose were all measured. The researchers used the student t-test and the Chi-square test to see if lower urinary tract symptoms were linked to pyuria (WBCs/HPF), hematuria (RBCs/HPF), and bacteriuria (>100,000 CFU/mL). A glucose oxidase technique was used to determine fasting blood glucose levels (Biolabo Company, France). Enzymatic assays (Human, Germany) were used to evaluate creatinine concentrations, whereas an assay kit developed by Biolabo Company, France, was used to determine urea and uric acid concentrations. Pyuria (expressed as ≥ 10 WBCs/high power field), hematuria (expressed as more than 5–10 RBCs/high power field), and bacteriuria (expressed as the number of cells/high power field) were all detected during the general urine examination (GUE). When bacteriuria levels surpassed 100,000 CFU/ml and lower urinary tract symptoms were present, it was thought that the patient had a urinary tract infection. Pyuria with a high level of bacteriuria (>105 colony-forming units (CFU)/mL) was regarded as a sign of a urinary tract infection (UTI) and was expressed as a proportion of infected patients. "Pyuria without obvious bacteriuria" is referred to as "sterile" pyuria. Ten mL of urine was centrifuged at 400 g for 5 minutes to be analyzed microscopically. Pyuria is still defined as ≥5 WBCs per high-power field (HPF) in urine microscopy of centrifuged urine. Hematuria was defined as "red blood cells in the urine induced by an infection" if red blood cells were visible in urine and red blood cells were detected at ≥3/HPF in microscopy [16,17].

Ethical consideration

The study protocol was approved by the College of Pharmacy, Mustansiriyah University's Scientific and Ethics Committee, as well as the Scientific Committee of the National Diabetes Center. All participants have agreed upon the research purpose, and the consent form has been signed. Participants were only considered if they signed informed consent forms and met the following criteria.

Statistical analysis

The Statistical Packages for Social Sciences, version 27 (SPSS-27), was used to analyze the data. Simple frequency, percentage, mean, and standard deviation measurements were used for data presentation. The difference between two independent measures We used a t-test or the difference between paired observations to examine the significance of distinct means in a paired t-test (or two dependent means). The Chi-square test (c^2-test) was used to determine the significance of distinct percentage differences. The statistical significance was achieved when the P-value was either equal to or less than 0.05.

RESULTS

In this study, Table 1 shows that there were no statistically significant differences between the groups. Of the 55 patients included in the study, 25 were men, and 30 were women.

Table 1: Baseline characteristics for control and Grape seed proanthocyanidin extract groups in type 2 diabetic patients with recurrent UTI.

Baseline characteristics		Control	GSPE	*p*-value
Age (years)	30-39	10 (37.0)	8(28.6)	0.780
	40-49	14(51.9)	17(60.7)	
	50-59	3(11.1)	3(10.7)	
		42.7±6.1	42.8±6.6	
Gender	Male	14(51.9)	11(39.3)	0.349
	Female	13(48.1)	17(60.7)	
Number of UTI during last six months	2	15(55.6)	16 (57.1)	0.691
	≥3	12 (44.4)	12(42.9)	
Duration of DM	<1year	14(51.9)	15(53.6)	0.821
	1-4	11(40.70)	12(42.9)	
	≥5 years	2(7.4)	1(3.6)	
Marital status	Single	2(7.4)	3(10.7)	0.669
	Married	25(92.6)	25(89.3)	
Education	Read & write	5(18.5)	3(10.7)	0.621
	Primary	4(14.8)	4(14.3)	
	Secondary	8(29.6)	6(21.4)	
	College	10(37.0)	15(53.6)	
Income (US $)	<500US$	8 (29.6)	10(35.7)	0.352
	≥500	14(51.9)	15(53.6)	
	≥750 US $	5(18.5)	3(10.7)	
		516.7±213.5	473.2±185.8	

Values were expressed as frequencies, percentages, and mean±SD. Chi-square test (χ^2-test) at <0.05 level.

The A group was formed by 14 men and 13 women, with a mean age of 42.7±6.1 years; the B group was formed by 11 men and 17 women, with a mean age of 42.8±6.6 years. Fasting plasma glucose, creatinine, uric acid, and urea concentrations in the GSPE group were shown to be statistically non-significant (p>0.05) by comparison to control groups in the present investigation, which used the student t-test (Table 2).

Table 2: Grape seed proanthocyanidin extract effect on glycemia and renal function in type 2 diabetic patients with recurrent UTI

Parameters	Control		GSPE	
	Baseline	After 12 weeks	Baseline	After 12 weeks
FBG (mg/dl)	165.52±15.16	148.04±10.40*	166.5±34.78	142.36±22.85*
Creatinine (mg/dl)	0.794±0.083	0.765±0.072 *	0.789±0.087	0.747±0.085 *
Urea (mg/dl)	27.14±4.21	26.82±4.29	28.74±4.58	24.91±3.60 *
Uric acid (mg/dl)	3.93±0.59	3.57±0.54 *	4.24±0.67	3.59±0.46 *

Data were presented as Mean±SD. * represent significant difference (p<0.05) between pre and post-treatment within the same group. There is no significant difference between the control and treatment groups.

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 GSPE for 12 weeks compared to control (Tables 3 and 4).

Table 3: Effect of Grape seed proanthocyanidin extract on pyuria and hematuria in type 2 diabetic patients with recurrent UTI

Parameters	Control		GSPE	
	Baseline	After 12 weeks	Baseline	After 12 weeks
Pyuria changes (WBCs/HPF)	17.15±5.40	16.26± 5.56	17.82±4.50[a]	2.25±1.11*[b]
Hematuria changes (RBCs/HPF)	4.81±2.00	4.30±2.02	4.64±1.54[a]	0.68±0.82 *[b]

Data were presented as mean±SD.* significant difference (p<0.05) comparing pre and post-treatment within the same group. Data with non-identical superscript letters (a,b) among treatment group are significantly different (p<0.05) compared with a control group.

Table 4: Effect of Grape seed proanthocyanidin extract on bacteriuria in type 2 diabetic patients with recurrent UTI

Bacteriuria changes (>10^5 CFU/mL= infected)		Control	GSPE
		n(%)	n(%)
Bacterial infection Bacteriuria changes (>10^5	Bacteria found	27(100)	28(100)
CFU/mL: infected) at Baseline	No	--	--
Bacterial infection bacteriuria changes (>10^5	Bacteria found	21(77.8)	2(7.1)*
CFU/mL: infected) after 12 weeks	No	6(22.2)	26(92.9)

* Significant difference between percentages using Chi-square test (χ^2-test) at <0.05 level. CFU, colony-forming unit.

The number of recurrent UTI episodes recorded as planned at 12, 16, 20, and 24 weeks is shown in Table 5. In particular, during the trial, 7.1%, 7.1%, and 10.7% of the GSPE 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.

Table 5: Effect of Grape seed proanthocyanidin extract on recurrence of UTI in type 2 diabetic patients after 24weeks follow up

Recurrence of UTI		Control	GSPE
After 12 weeks	Infection	21(77.8)	2(7.1)
	No	6(22.2)	26(92.9)
16 weeks	Infection	7(25.9)	-
	No	20(74.1)	28(100)
20 weeks	Infection	13(48.1)	2(7.1)
	No	14(51.9)	26(92.9)
24 weeks	Infection	9(33.3)	3(10.7)
	No	18(66.7)	25(89.3)

Values were expressed as frequencies and percentages.

DISCUSSION

Infections of the urinary system are common in people with type 2 diabetes, who frequently contract urinary system infections. High urine glucose levels can promote the growth of dangerous germs, impaired bladder emptying due to autonomic neuropathy, poor metabolic control due to diabetes, and a variety of immune system weaknesses. Higher bacterial growth and decreased micturition clearance by diabetic patients with UTIs can all contribute to the pathogenesis [18]. Deficiencies in the immune system, including humoral, cellular, and innate immunity, may contribute to UTI formation in diabetics. Bladder dysfunction occurs in 26–85% of diabetic women with asymptomatic bacteriuria (ASB), and it should be considered in all diabetic UTI patients [19]. Recurrent urinary tract infections (rUTIs) are described as more than two infections in six months or three infections in a year, with at least two weeks between infections. These are caused by the same pathogen and can be triggered by a relapse due to insufficient (persistence) or reinfection (new source) treatment. rUTIs are caused by a number of factors, including a weakened immune system and the presence of virulence factors in the body [20]. Urinalysis is a battery of tests performed on patients with suspected UTI [21]. Prioritizing treatment for urinary tract infections entails eliminating the causative pathogen, preventing and treating the infection's consequences, implementing targeted antimicrobial therapy based on culture and sensitivity findings, and preventing the recurrence of urinary tract infections [22]. Early diagnosis, treatment, and prevention are crucial for preventing recurrent UTIs; basic measurement failures may necessitate the administration of low-dose daily antibiotics for six months or longer. One study found that weekly prophylaxis was more effective than monthly prophylaxis, but no such findings were seen when daily and weekly prophylaxis were compared [23]. However, repeated use of antibiotics can cause dysbiosis of vaginal and intestinal normal flora, as well as antibiotic resistance due to bacteria's high mutation and horizontal gene transfer abilities. Moreover, uropathogens adopt many strategies to survive in the bladder, including starvation and immunological responses. Uropathogens change shape, infiltrate uroepithelial cells, and build biofilms in order to survive and re-infect. Bacterial

communities can thrive in a safe environment free of antimicrobial agents, immunological reactions, and other pressures thanks to extracellular DNA and other sticky fibers. Therefore, it is time to find new ways to prevent and treat UTIs [24]. Pharmaceutical plants have a lot of different chemicals that give them their unique properties. These chemicals include alkaloids, anthraquinones, flavonoids, glycosides, phenols, saponins, steroids, sterols, tannins, terpenoids, triterpenoids, phytosterols, hydrocarbons, mono- and sesquiterpenes, phlorotannins, and many more. In order to treat UTI, flowers, leaves, bark, fruit, seeds, and even whole portions of medicinal plants were consumed [25**].** The levels of pyuria, hematuria, and bacteria in the blood of people with type 2 diabetes who were treated with proanthocyanidin were checked three months later. They were statistically significant decrease than they were before treatment. This was compared to the pre-treatment values for the proanthocyanidin group of type 2 diabetics, and the decrease in comparison to the control group was statistically significant (using a student t-test). *S. aureus* was the most susceptible to GSPE, followed by *K. pneumoniae* and *E. coli* [26]. Ranjitha *et al*. demonstrated GSPE's efficacy against foodborne bacteria [26]. In the same conditions, microbes broke down grape seed polyphenols more slowly than cranberry polyphenols. This was in line with the fact that grape seed polyphenols were more effective at killing bacteria, especially *Bacillus cereus* (*B. cereus*), *Bacillus subtilis* (*B. subtilis*), *Staphylococcus aureus* (S. aureus), *Bacillus coagulans* (*B. coagulans*), *Escherichia coli* (E. coli), and *Pseudomonas aeruginosa* (*P. aeruginosa*) [27,28]. Grape seeds contain high levels of proanthocyanidins, which have piqued consumer interest due to the potential health benefits they may provide. Studies [28,29] show that antioxidant proanthocyanidins remove reactive oxygen and nitrogen species in vitro, change the function of the immune system and the activation of platelets, and help blood vessels relax by increasing the release of nitric oxide (NO) from the endothelium. The proanthocyanidins in grape seed have a beneficial long-term effect on glucose homeostasis. Grape Seed Proanthocyanidin Extract significantly affected FPG serum levels and HbA_{1c} compared to pre-treatment levels, according to the paired t test, indicating a non-significant decrease compared to the control group. This is in line with the study of Asbaghi *et al*., 2020 [30], and agrees with Mohammad *et al.*, 2021 [31], who said FPG levels were shown to be unaffected by GSPE when compared with the placebo group according to the findings of the current investigation. The variety of ways in which grapes and grape products may improve glycemic indices is because of the huge number of bioactive substances that have been demonstrated to have a positive influence on insulin and glucose metabolism, oxidative damage, β-cell mass, and β-cell function [32]. Grape seed proanthocyanidin extract (GSPE) is a complex multi-organ protective mixture that includes flavonoids, non-flavonoids and proanthocyanidins. For example, GSPE helps protect the heart, liver, brain and kidney from obesity generated in rats by a high-fat diet (HFD). High-dose GSPE also showed that its anti-oxidant and anti-inflammatory activities have improved the kidney damage of diabetic rats' type 2 [33]. The result of the current study disagrees with the result of Sano (2017), according to creatinine, urea and uric acid, who found a non-significant result according to baseline [34] and also with Amin *et al. (*2018), who disagree with the current study results about creatinine, uric acid, and urea, who said they have a significant result with creatinine, urea and uric acid compared to control [35]. Meanwhile, Yusong *et al*. (2020) agree with the study result that serum creatinine, blood urea nitrogen and uric acid were also significantly decreased compared to the baseline [36]. As a result, GSPE shows promise as a diabetic nephropathy therapy agent. It plays a crucial role in regulating antioxidant enzymes by activating the Nrf2-ARE signaling pathway. This pathway serves as a protective mechanism against oxidative and metabolic stress in the kidneys. By maintaining redox balance and mitigating cellular damage, GSPE contributes to shielding the kidneys from developing diabetic nephropathy, a common complication associated with diabetes [37]. A lot of information: During this study, 3.5%, 7.1%, and 10.7% of the people who were in the grape seed proanthocyandin extract group had UTIs during the 4-, 5-, and 6-month follow-up periods, respectively. Urinary tract infections (UTIs) are primarily caused by *Escherichia coli (E. coli*) bacteria, accounting for the majority of cases. On their surfaces, adhesin colonization factors called fimbriae (pili) are produced. Adhesions on fimbrial tips work as lectins to connect bacteria to uroepithelial cell sugar receptors. Most adhesins are either PapG mannose-resistant (MR) or FimH mannose-sensitive (MS) on P-fimbriae. P-fimbriated E. coli are linked to bladder and kidney infections, especially pyelonephritis, which can be fatal. Proanthocyandin mostly stops P-fimbriated E. coli from sticking together. The unique double A-type connections between the molecules may play a key role in the process of stopping adhesion [38]. Grape seed proanthocyanidin extract is the stronger antibacterial agent and has an anti-adhesion effect. A high dose of this antioxidant is both safe and effective, and it can be used in clinical trials to help maintain renal function over the long term. Nephropathy, neuropathy, and retinopathy are all major secondary consequences of diabetes mellitus; renal function was also recovered, which resulted in lower albuminuria in the treated group compared to the untreated group [39]. Despite the fact that no interventional trials have been conducted to examine the efficacy of grape seed proanthocyanidin extract on recurrent UTI in type 2 diabetes patients, there was a significant reduction in pyuria, bacteria, and hematuria when compared to the baseline and control groups, as well as a reduction in the percentage of recurrent UTI occurrence through the follow-up period.

Limitations of the study

We must consider the limitations of this study when interpreting its findings. Future research could address the two major limitations identified in this study. First, the study should concentrate on comprehending the impact of grape seed proanthocyanidin extracts on the late adverse effects experienced by patients with rUTI, requiring a large-scale investigation and an extended

study period. Second, try using grape seed proanthocyandin extract on other types of UTIs, such as complicated ones and those that are more difficult to treat.

Conclusion

Supplements containing grape seed proanthocyandin extract can help cure and prevent the recurrence of urinary tract infections in type 2 diabetes. There is no significant difference in FBG between the experimental and control groups. Research demonstrates no therapeutic effect on renal function, but it does yield positive effects. This would reduce the risk of diabetes-related kidney damage.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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