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Green tea as an adjunctive therapy for treatment of acute uncomplicated cystitis in women: A randomized clinical trial

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ABSTRACT

Background: and purpose: Different in vitro studies have reported the antimicrobial effects of green tea catechins and also their synergistic effects with trimethoprim–sulfamethoxazole against *E. coli*. The aim of the present study was to evaluate the efficacy of green tea as an adjunctive therapy to standard antimicrobial treatment in women with acute uncomplicated cystitis.

Materials and methods: In this blinded randomized trial, 70 patients were assigned to receive four 500 mg capsules of green tea or starch as placebo daily for three days along with trimethoprim–sulfamethoxazole. The presence of acute uncomplicated cystitis symptoms was recorded and urinalysis was performed.

Results: Women in the green tea group showed a statistically significant decrease in the prevalence of cystitis symptoms and a statistically significant improvement in the urinalysis results except for hematuria after 3 days of treatment.

Conclusion: Green tea was an effective adjunct to trimethoprim–sulfamethoxazole to treat acute uncomplicated cystitis in women.

1. Introduction

Urinary tract infections (UTIs) are of the most common infections occurring frequently in both community and hospital settings, and result in high annual healthcare costs [1]. UTIs are known as diseases of females because of sex-based differences in anatomic and physiologic characteristics [2]. The bladder infections in healthy premenopausal and non-pregnant women with normal structure of genitourinary tract are referred to as acute uncomplicated cystitis which is classified as lower UTI. In women, uropatogenic *Escherichia coli* (*E.coli*) is the most common cause of uncomplicated UTIs, and it is responsible for 75–95% of these infections [3].

Trimethoprim–sulfamethoxazole (co-trimoxazole) is an inexpensive, well tolerated, and effective antibiotic that has been traditionally used to treat acute uncomplicated cystitis as the first line choice. However, co-trimoxazole resistance among *E. coli* strains has significantly increased worldwide in recent years. Considering this fact, it is recommended that if the prevalence of co-trimoxazole resistance among *E. coli* strains is equal to or more than 20% in a region, other first line antimicrobial agents should be chosen [4]. High rate resistance to co-trimoxazole causes poor outcome, increases drug costs, and limits the use of this valuable antibiotic. Also, co-trimoxazole resistance has been related to the emergence of multidrug-resistant uropathogens [5]. Consequently, a new interest is grown to use herbs with antibacterial activity against uropatogenic *E. coli* to treat acute uncomplicated cystitis and reduce antibacterial resistance [6].

Green tea is a type of tea that is made from non-fermented leaves of the *camellia sinensis* L. This safe, cheap, available and popular beverage is consumed worldwide, traditionally in Asian countries [6,7]. This ancient plant has various health benefits such as anti-inflammatory, antiarthritic, antibacterial, antiangiogenic, antioxidative, antiviral, and neuroprotective effects [7]. Most of these health beneficial properties of green tea are attributed to its polyphenolic compounds, particularly catechins. The major green tea catechins are (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC), and (−)-epigallocatechin-3-gallate (EGCG) [8,9]. EGC and EGCG have the highest amounts in green tea and also have the greatest antimicrobial effects, but only EGC is excreted in urine [1]. It has been reported that 3.3% of

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ingested EGC is excreted in urine [9].

Some in vitro studies have shown the antimicrobial effects of catechins against *E. coli* and also the synergistic effects between catechins and antibiotics such as co-trimoxazole and quinolones against *E. coli* [6]. Furthermore, it has been proposed that the amount of EGC excreted in urine after ingesting one cup of 7.5 g green tea would be good enough to produce minimum inhibitory concentrations of EGC [1]. To the best of our knowledge, since there has been no human study to investigate the effects of green tea on UTIs, the present study was designed to evaluate the efficacy of green tea as an adjunctive therapy to standard antimicrobial treatment in women with acute uncomplicated cystitis.

2. Materials and methods

2.1. Study design, setting, and participants

This randomized, blinded, placebo-controlled trial was conducted in Besat Clinic affiliated to Kerman University of Medical Sciences, Kerman, Iran from August to October 2017. The patients, physician, and outcome assessor were blinded to intervention assignment. The study protocol was approved by the ethical committee of Kerman University of Medical Sciences. In addition, the trial was registered in the Iranian Registry of Clinical Trial (IRCT201506156026N3). All the participants signed an informed consent form before beginning the study.

The response rate to co-trimoxazole was assumed to be about 50%, and it was expected that the rate would rise to 80% by adding green tea. Therefore, a sample size of 35 patients in each group was required to detect this change with 80% power at an α level of 0.05. Fig. 1 shows the CONSORT flow diagram of this study.

Healthy premenopausal, non-pregnant adult women (in the age range of 18–50 years) with acute uncomplicated cystitis were included in the study. Women with recurrent urinary tract infection, vaginitis irritation or discharge, underlying conditions that increase the risk of infection such as anatomic abnormality and diabetes, and green tea hypersensitivity were excluded from the trial. Regular green tea drinkers were also excluded. An infectious disease specialist diagnosed acute uncomplicated cystitis based on medical history, physical examination, clinical manifestations, and urinalysis. Also, he assessed the presence of vaginitis or urethritis.

2.2. Intervention and assessments

The study participants were recruited by an infectious disease specialist after the diagnosis of acute uncomplicated cystitis was made, and then they were assessed for eligibility. The eligible participants were allocated to one of the two study groups in a 1:1 ratio. Allocation was by block randomization with a block size of four. A person (not involved in the trial) generated allocation sequence. In this way, the allocation was concealed from the researchers. After collecting the first urine sample, the enrolled patients received four 500 mg capsules of spray-dried aqueous extract of green tea (green tea group) or starch as placebo (matching regarding shape, color, and outer packaging) (placebo group) daily in the evenings for three days. Also, all the participants received standard antimicrobial therapy for acute uncomplicated cystitis as two 480 mg tablets of co-trimoxazole twice daily for three days. The green tea capsules were administered in the evenings because of EGC being retained all night in the bladder; therefore, its effectiveness was enhanced [10]. Moreover, after ingesting green tea, more than 90% of urinary EGC is excreted in the first 8 h [9]. The spray-dried aqueous extract of Lahijan green tea was purchased from Soha Jisa Company, Salmanshahr Industrial Area, Mazandaran, Iran. Each gram of the spray-dried aqueous extract of green tea contained 283.6 ± 10.57 mg gallic acid of total phenolic content measured by the Folin-Ciocalteu method [11] and 65.63 ± 4.17 mg of EGC

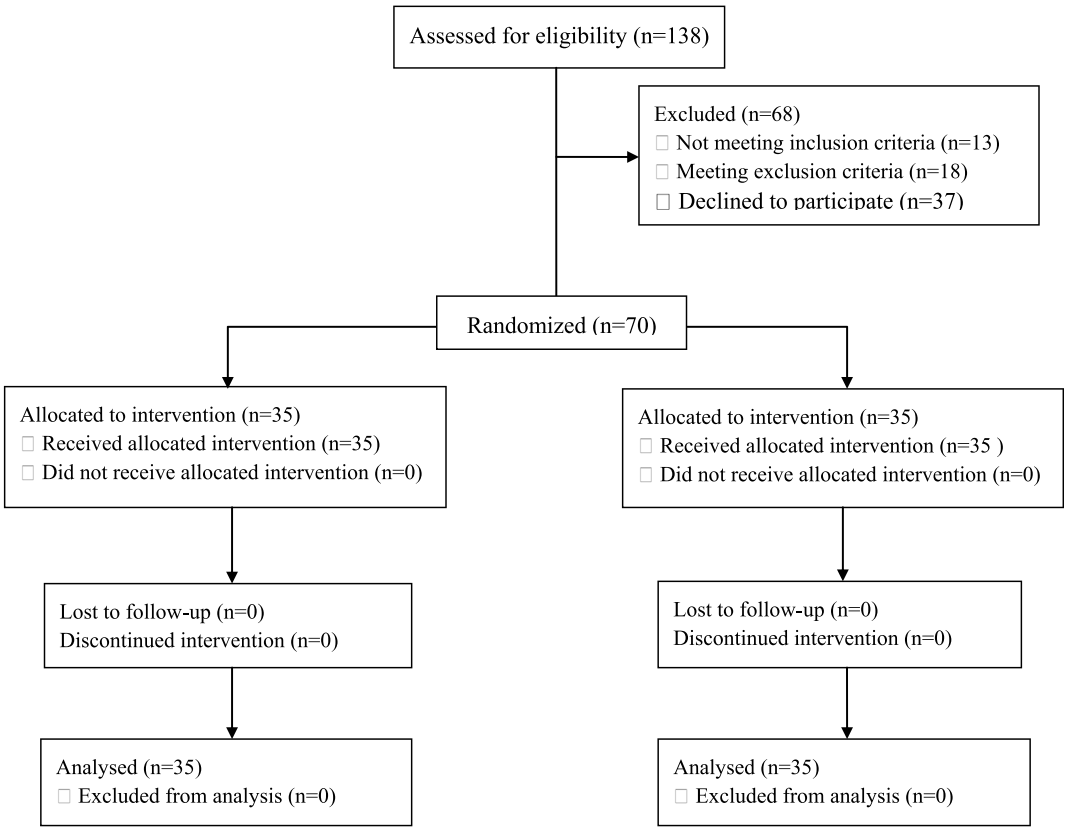

Fig. 1. CONSORT flow diagram of the study participants.

determined by high-performance liquid chromatography (HPLC) method [12].

The presence of acute uncomplicated cystitis symptoms (dysuria, frequent urination, suprapubic pain, blood in urine, and back pain) was recorded at baseline and also daily for 3 days after receiving the intervention. Additionally, possible side effects of the treatments were recorded at each time point. Also, clean-catch midstream urine specimen was collected from each participant at baseline and also on the fourth day after receiving the intervention. The urine samples were sent to Besat Laboratory for urinalysis. It should be noted that the participants came to the clinic at baseline and on the fourth day, but at the other time points, the researcher phoned them for recording symptoms and possible side effects. If the symptoms of cystitis or abnormal urinalysis results were not resolved until the fourth day after the treatment, the patients would be referred to the physician again for further evaluations. Additionally, the patients were asked to return to the clinic after two, four, and six weeks following the enrollment and to make the physician assess the symptoms of recurrent uncomplicated cystitis.

2.3. Statistical analysis

The Statistical Package of Social Science (SPSS) version 20 was used for all the analyses. An independent samples *t*-test was employed to compare the means of the quantitative data. Generalized estimating equation was used to compare binary data (cystitis symptoms) over the time between the green tea and placebo groups. Chi-square test was applied to evaluate the differences in qualitative data (such as urinalysis data) at baseline and after 3 days between the two groups. P-values less than 0.05 were considered statistically significant.

3. Results

Among 107 eligible patients, only 70 patients completed this trial. The mean ± SD of the participants' age was 33.91 ± 11.57 years in the placebo group and 30.60 ± 10.58 in the green tea group. No statistically significant difference regarding age was detected between the two groups. The duration of the symptoms before receiving the treatment was 14.49 ± 7.84 days in the placebo group and 10.89 ± 9.05 in the green tea group. Also, there was not any statistically significant difference between the two groups in this regard.

Women in the green tea group showed a statistically significant decrease in the prevalence of cystitis symptoms in each time point after initiating the treatment in comparison with the placebo group. Table 1 presents the prevalence of cystitis symptoms over the time in the two groups. Meanwhile, the addition of the green tea resulted in a statistically significant improvement in the urinalysis results (abnormal urine color, pyuria, and bacteriuria) [4,13] except for hematuria after 3 days of the treatment. Table 2 demonstrates some urinalysis data at baseline and on the fourth day in both groups after receiving the intervention. The other urinalysis data of all the participants including protein, glucose, ketones, bilirubin, and epithelial cells were within the normal range at each time point.

Table 1
Prevalence of cystitis symptoms over the time in green tea and placebo groups.

Time point	Group	Presence of symptoms (%)	[a] Exp (B)	95% [b] CI for Exp(B)	[c] P-value
Baseline	Green tea	68%	0.71	0.48–1.07	0.099
	Placebo	75%	1		
After 1 day	Green tea	61%	0.55	0.38–0.78	0.001
	Placebo	74%	1		
After 2 days	Green tea	34%	0.26	0.17–0.39	0.0001
	Placebo	67%	1		
After 3 days	Green tea	2%	0.01	0.003–0.03	0.0001
	Placebo	63%	1		

[a] Exponential beta.
[b] Confidence interval.
[c] Based on generalized estimating equation.

No one in the green tea group and also placebo group (among the patients who responded to co-trimoxazole therapy) showed the symptoms of recurrent cystitis two weeks after the enrollment. After four weeks, 1 (2.86%) of the 35 patients in the green tea group, and after six weeks, 2 (15.38%) of the 13 patients who responded to co-trimoxazole therapy in the placebo group had the symptoms of recurrent cystitis.

Seven patients in the placebo group and six in the green tea group reported mild nausea that was resolved within two days. There was no statistically significant difference in the incidence of nausea between the two groups.

4. Discussion

The present study demonstrated that green tea as an adjunctive therapy had significant effects on treating acute uncomplicated cystitis in women. This result could be related to antibacterial effects of green tea EGC and its synergistic effects with antibiotics. Different in vitro studies have reported the antimicrobial effects of green tea catechins against *E. coli* with different mechanisms [1,6,14,15]. In one of these studies, it was found that 99% of the *E. coli* strains isolated from UTIs were susceptible to the green tea extract at a concentration of ≤ 4.0 mg/ml and to EGC at a concentration of ≤ 0.72 mg/ml [1]. Additionally, some in vitro studies have shown the synergistic effects between green tea catechins and co-trimoxazole against *E. coli* [6,16,17]. Yet, Neyestani et al. revealed that the green tea extract had synergistic effects with sulfamethoxazole in a dose-dependent manner [17].

In the present study, in the placebo group, 63% of the patients remained symptomatic, 37.1% had bacteriuria, and 57.1% had pyuria on urinalysis after 3 days of co-trimoxazole therapy. These findings can suggest high prevalence of co-trimoxazole resistance among uropathogenic *E. coli* strains causing acute uncomplicated cystitis in women in Kerman. Previous in vitro studies in Iran have reported that more than 47% of the *E. coli* isolates from patients with UTIs were resistant to co-trimoxazole suggesting that co-trimoxazole should not be used to treat UTIs [18,19]. However, these reported resistance rates were based on urine samples obtained from men or women, outpatients or inpatients, those with complicated or uncomplicated or recurrent UTIs, and upper or lower UTIs. Therefore, these reports can overestimate the rates of resistance among women with acute uncomplicated cystitis [3]. However, in the current study, in the green tea group, almost all the patients responded to treatment for its antimicrobial effects and/or its synergistic effects with co-trimoxazole. If the response rates were related to the synergistic effects of EGC, it could be proposed that adding green tea to co-trimoxazole therapy could be a way to decrease and control the rates of co-trimoxazole resistance among uropathogenic *E. coli* strains [20]. In addition, there was not any significant difference between the two groups regarding hematuria. However, it should be considered that bacteriuria and pyuria are more valuable laboratory diagnostic parameters for UTI than hematuria [21]. Moreover, the percentage of the patients who had recurrent symptoms six weeks after the enrollment was lower in the green tea group in comparison with that in the placebo group. Accordingly, it could be proposed that green tea might reduce the incidence of recurrent uncomplicated cystitis. However, further studies are required to confirm this finding.

In the present study, nausea was the most common adverse effect that was recorded. Yet, there was not any significant difference in the occurrence of nausea between the placebo and green tea groups. Therefore, it could be related to co-trimoxazole which has been previously reported [22].

Finding medicinal plants to treat UTIs is required because many women with UTIs prefer using home remedies and do not seek medical help immediately [23]. Therefore, some studies evaluated different herbs for this purpose. In one of these studies, Ivanov et al. have reported that using the combination of centaury herb, lovage root, and

Table 2
The urinalysis data at baseline and on fourth day after receiving intervention in green tea and placebo groups.

Examination	Group					
	Baseline Number (Percent)			After 4 days Number (Percent)		
	Green tea	Placebo	[a] P-value	Green tea	Placebo	[a] P-value
[b] Abnormal urine color	24 (68.6%)	27 (77.1%)	0.296	0 (0.0%)	13 (37.1%)	0.0001
[c] Pyuria	35 (100%)	33 (94.3%)	0.246	0 (0.0%)	20 (57.1%)	0.0001
[d] Hematuria	30 (85.7%)	31 (88.6%)	0.500	2 (5.7%)	6 (17.1%)	0.130
[e] Bacteriuria	29 (82.9%)	32 (91.4%)	0.239	0 (0.0%)	13 (37.1%)	0.0001

[a] Based on Chi-square test.
[b] Normal: straw [4].
[c] ≥ 5 white blood cells per high-power field of centrifuged urine [4,13].
[d] ≥ 3 red blood cells per high-power field [13].
[e] ≥ 5 bacteria per high-power field [13].

rosemary leaves was a safe and effective approach to manage UTIs [23]. In another study, Shaheen et al. have concluded that cranberry had a therapeutic value to treat UTIs [24]. Moreover, the present study introduced the green tea as an effective adjunctive therapy with antimicrobial property to treat acute uncomplicated cystitis and somewhat confirmed the suggestion of Reygaert et al. that drinking only one cup of green tea could have beneficial effects on UTIs because it made a level of ECG in urine that was sufficient to inhibit *E. coli* growth [1].

The present study had some limitations. The sample size was relatively small. Larger clinical trials are needed to reach more accurate conclusions. Furthermore, it is suggested to conduct randomized clinical trials that use green tea as a primary treatment not an adjunctive therapy to distinguish its antimicrobial effects from its synergistic effects. Additionally, in the present study, urine culture and susceptibility test were not used. It might be better to perform urine culture to identify specific organisms causing UTIs and also susceptibility test to determine the sensitivity of the uropathogens to co-trimoxazole. However, it should be noted that a urine culture is not necessary for the diagnosis of acute uncomplicated cystitis. Notable to say that using urinalysis is a more cost-effective approach [3,4]. Also, bacterial susceptibility to different antibiotics is usually based on serum concentrations of those drugs. However, the concentrations of antibiotics achieved in urine may be 20 to 100 times greater than those in serum. Therefore, antibiotics with such high concentrations in urine can effectively treat intermediately susceptible or even resistant uropathogens [4].

5. Conclusion

It was concluded that green tea was an effective adjunct to co-trimoxazole to treat acute uncomplicated cystitis in women. However, further studies are required to confirm the results of the present study.

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Conflicts of interest

The authors declared that there is no conflict of interest.

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