

## The Role of Cranberry in Preventing Urinary Tract Infection in Children; a Systematic Review and Meta-Analysis

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### Abstract

#### Background

Although effectiveness of cranberry for preventing urinary tract infection (UTI) has been reported in Iranian traditional medicine and recent studies there is still controversy in this regard. Therefore, the present study was designed with a meta-analytic approach aiming to evaluate the effect of prophylaxis prescription of cranberry in prevention of UTI in children.

#### Materials and Methods

In this study, a thorough search was performed in Medline, Embase, Web of Sciences, Scopus and CINHALL databases by the end of August 2017. Using keywords related to urinary tract infection combined with words related to cranberry, search strategy was designed. The articles were summarized and finally, the role of cranberry extract consumption in decreasing the incidence of UTI was evaluated by reporting odds ratio (OR), and 95% confidence interval (95% CI).

#### Results

In the end, 10 studies were included (414 cases in control group and 380 in cranberry extract treatment group). Analyses showed that prescription of cranberry significantly reduced the odds of UTI manifestation in children compared to placebo (OR=0.31; 95% CI: 0.21 to 0.46;  $p<0.0001$ ). On the other hand, it was determined that effectiveness of cranberry in decreasing UTI manifestation was similar to antibiotic treatment (OR=0.75; 95% CI: 0.34 to 1.70;  $p=0.495$ ).

#### Conclusion

In the present study, it was determined that prophylaxis prescription of cranberry extract leads to prevention of UTI manifestation in children and its effectiveness is similar to that of antibiotics.

**Key Words:** Children, Cranberry, Prevention, Traditional Medicine, Urinary Tract Infections.

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## 1- INTRODUCTION

Urinary tract infection (UTI) is a common problem in childhood and between 2% and 8% of the children experience UTI at least once before turning 7 years old (1). In a considerable fragment of these children recurrence of UTI is observed (2). The standard treatment for preventing UTI recurrence in high-risk children (such as children with obstructive diseases and vesicoureteral reflux) is administration of low-dose antibiotics as prophylaxis. However, a systematic review in 2011 showed that long-term use of antibiotics has low effectiveness in prevention of UTI (3). Therefore, researchers are looking for other methods for this purpose. Using alternate treatments such as natural compounds and probiotics has been suggested in numerous studies. The effect of probiotics in controlling UTI has been dismissed in a systematic review published in 2017 (4). However, there is still controversy regarding natural compounds.

In Iranian traditional medicine, special attention has been paid to using cranberry or *Vaccinium macrocarpon* for prevention of diseases such as diabetes, eye diseases, bladder diseases and different infections. In Iranian traditional medicine books, it has been said that cranberries are nutritious, diuretic, and antiseptic and reduce blood sugar. Additionally, it improves the function of organs and has a healing effect especially regarding cough, nausea, stomach ache, intestine dysfunction, diarrhea, bladder dysfunction, and urinary incontinence in children. In external use, this product can be consumed for mouth and throat disinfection, relieving eye edema, and treating skin diseases such as pimples, injuries, and burns (as lotion, compress and local bath) (5). Its roots are used for disinfecting wounds and their rapid healing. Recent studies have also shown that prophylaxis use of cranberry can reduce the occurrence of UTI in both

children and adults (6-11). However, due to the conflicts in this field a consensus has not been reached in this regard. One of the strategies for reaching a final decision is performing a meta-analysis (12-17). Although in recent years some meta-analyses have been done on the effectiveness of cranberry in preventing UTI (8, 10, 18-20), presence of limitations such as more focus on adult population, presence of obvious publication bias, and finally inclusion of few pediatric studies all indicate an aching need for performing another meta-analysis. Thus, the present study was designed with a meta-analytic approach aiming to evaluate the effect of prophylaxis prescription of cranberry in prevention of UTI in children.

## 2- MATERIALS AND METHODS

### 2-1. Study design

The present meta-analysis gathered evidence from clinical trials that had evaluated the effectiveness of cranberry extract for UTI control in children based on Cochrane guideline.

### 2-2. Search strategy and selection criteria

To reach the aims of this study, a thorough search was performed in Medline, Embase, Web of Sciences, Scopus and CINHALL databases by the end of August 2017. Using keywords related to urinary tract infection combined with words related to cranberry, search strategy was designed. Initially, the query for searching in Medline database was designed and then modified to make it suitable for other databases. Search query in Medline database was as follows:

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("urinary tract infection"[Mesh] OR
"urinary tract infection"[TIAB] OR
"urinary tract infection therapy"[TIAB]
OR "urinary tract infections prevention
and control"[TIAB] OR "cystitis"[TIAB]
OR "pyelonephritis"[TIAB] OR "
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bacteriuria "[TIAB] OR "pyuria"[TIAB] OR "pyuric "[TIAB] OR "pyurias"[TIAB] OR "utis "[TIAB] OR "uti"[TIAB])) AND ("Vaccinium macrocarpon"[Mesh] OR "Phytotherapy"[Mesh] OR "Herbal Medicine"[Mesh] OR "Vaccinium macrocarpon"[TIAB] OR "Phytotherapy"[TIAB] OR "Herbal Medicine"[ TIAB] OR "Vaccinium macrocarpons"[TIAB] OR "macrocarpon, Vaccinium"[TIAB] OR "Cranberry"[TIAB] OR "Cranberries"[TIAB] OR "Herbal Therapy"[TIAB] OR "Herb Therapy"[TIAB])

In addition to the systematic search, a hand search was also performed in Google search engine, Google Scholar and the thesis section of proQuest database. In addition, the list of references in related articles were searched for finding more studies.

Inclusion criteria consisted of randomized clinical trials that had evaluated the effect of cranberry prescription in controlling UTI. Exclusion criteria were considered adult (age over 18 years) participants, patient follow-up of less than 2 months, lack of a control group (placebo group or antibiotic treatment group) and review articles.

### 2-3. Data synthesis

The records obtained in search were entered to endnote version 7.0 and duplicates were eliminated. Then, two independent researchers selected related studies by reading the title and abstract of the articles and reading the full article in the next step. Then using a checklist data of the studies were summarized. These data included information on indexing of articles, study population (age and gender), criteria for diagnosis of UTI and outcomes. The two researchers read the articles and recorded their data independently. Any disagreements were solved by discussion.

### 2-4. Quality control of the articles

Quality control of the articles was done based on Cochrane guideline. According to this guide, quality of the articles should be assessed based on 7 items and risk of bias in each item should be classified as low, unclear and high.

### 2-5. Statistical analyses

Analyses were done via STATA 14.0 statistical software. In the present study, 2 approaches were used for evaluating the effectiveness of cranberry extract prescription in controlling UTI. In the first approach, using the "metan" command in the statistical software, the role of cranberry extract consumption in decreasing the odds of UTI manifestation was evaluated by reporting odds ratio (OR), and 95% confidence interval (95% CI). In the second approach, the rate of UTI manifestation in the group treated with cranberry extract was compared to the control group using "metporp" command in STATA 14.0 software. Heterogeneity between the studies was evaluated using I-squared test (I-squared less than 50% indicates homogeneity of the studies) and publication bias was assessed via Egger's test. If studies were homogenous, fixed effect model was used and if not, random effect model was applied. It should be noted that in all analyses  $p < 0.05$  was considered the level of significance.

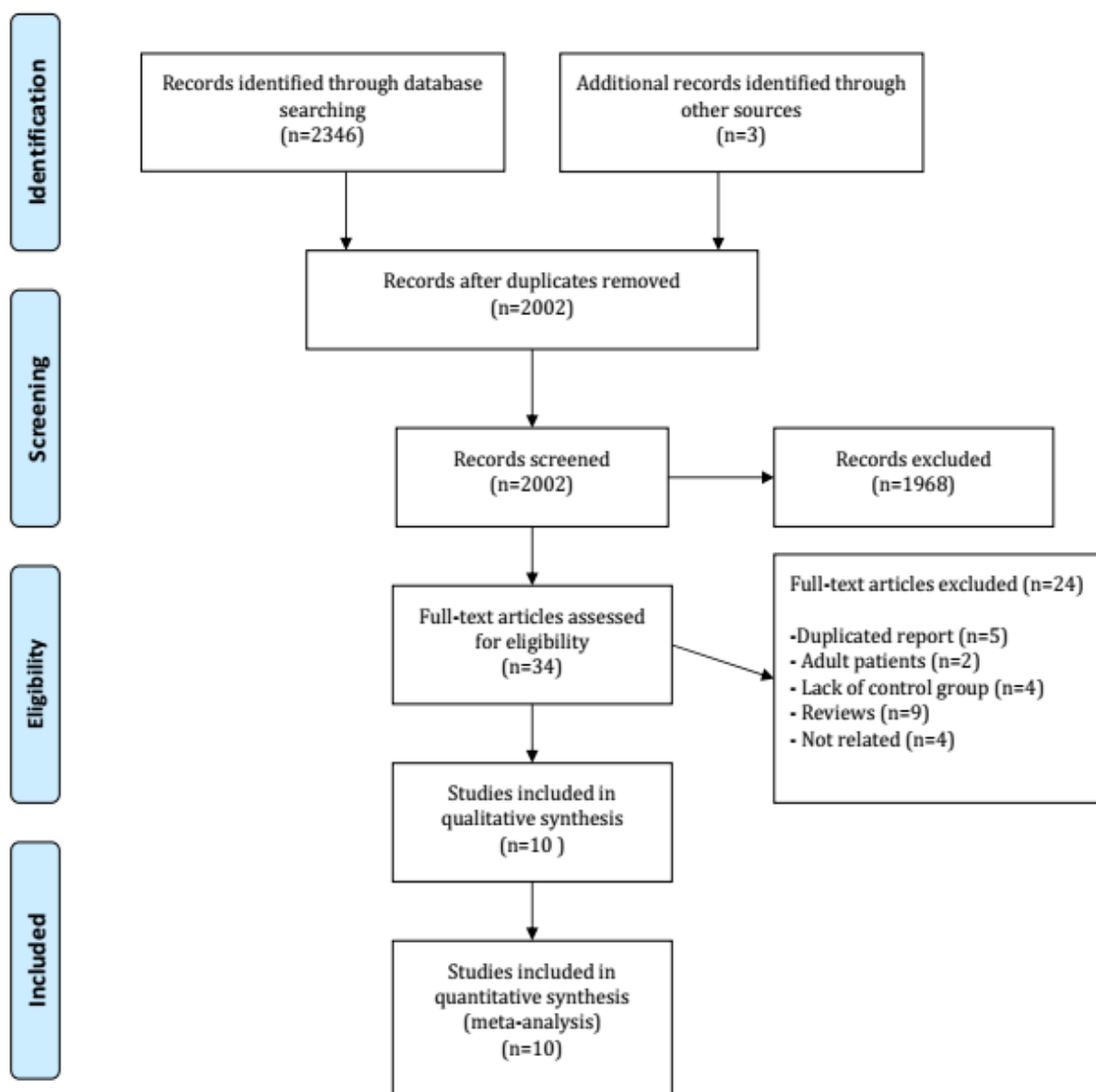
## 3- RESULTS

### 3-1. Characteristics

Searching in electronic databases yielded 2002 non-duplicate records. With the initial screening, 1958 articles were excluded and considering the inclusion and exclusion criteria, finally 10 studies were included (**Figure.1**) (9, 11, 18, 21-27). These studies consisted of 8 parallel clinical trials(9, 11, 18, 21, 22, 24, 25, 27) and 2 cross-over clinical trials (23, 26). These studies contained the data of 794

children (414 cases in the control group and 380 in the group under treatment with cranberry extract). Most of the studied children were girls (74.81%). 8 studies had compared the effectiveness of cranberry extract with placebo (9, 11, 18, 21-23, 25, 26), while comparison was done with antibiotics in 2 studies (24, 27). Duration

of treatment with cranberry extract was between 2 and 17 months. It should be noted that follow-up period was between 6 and 12 months in 8 studies (9, 11, 18, 21, 23, 25-27). **Table.1** depicts a summary of the characteristics of the articles included in the current study (*Please see table.1 in the end of paper*).



**Fig.1:** PRISMA flowchart of present study

### 3-2. Quality control and risk of bias

The quality of the studied articles has been presented in **Table.2** and **Figure.2A**. As can be seen, risk of bias regarding random sequence generation was low in all articles. It should be noted that in 40% of the articles there was a high risk of bias regarding blinding of outcome assessment (Please see Table.2 in the end of paper).

Publication bias was not present in the current study. Regression coefficient obtained from Egger's test was calculated to be -1.15 (95% CI: -4.30 to 1.99;  $p=0.42$ ), which indicates the absence of publication bias in the present study (**Figure.2B**).

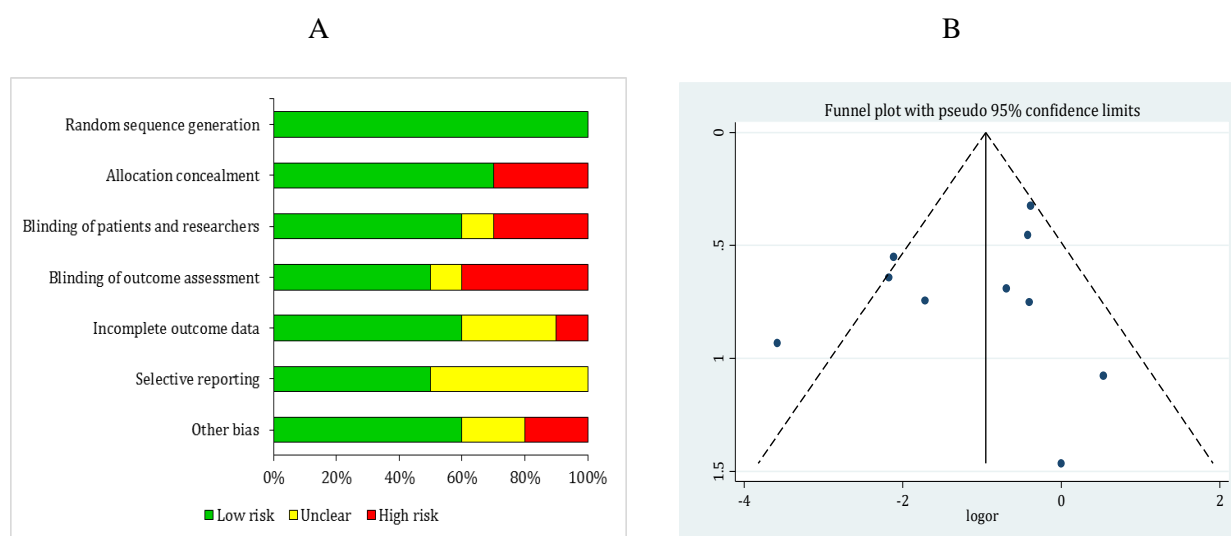
### 3-3. Effectiveness of cranberry extract consumption on UTI manifestation

There were 2 different types of control group in the included studies, one was placebo-receiving control group and the other was antibiotic-receiving control group. Therefore, the analyses of this section were also stratified based on control group type.

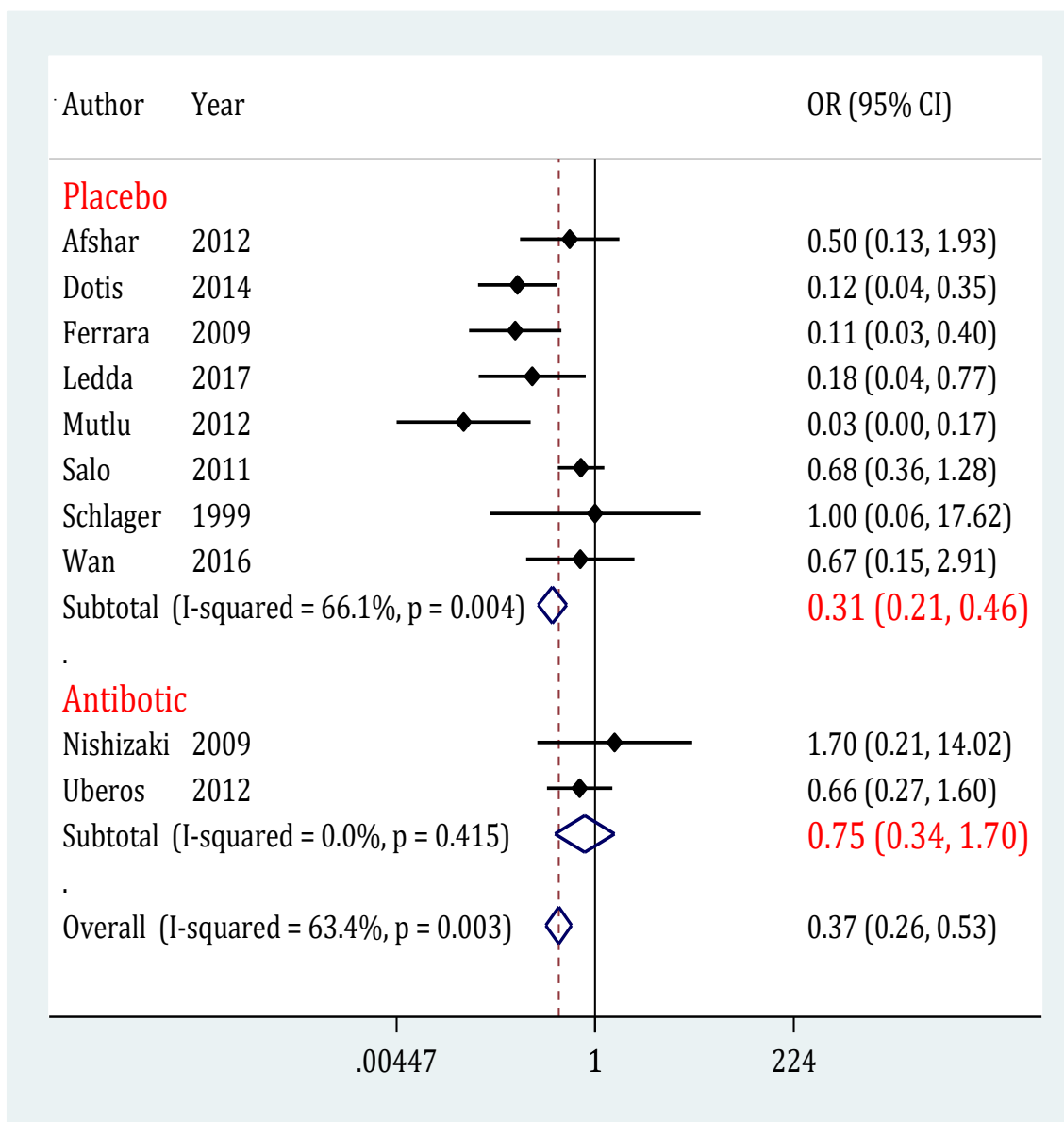
Analyses showed that prescription of cranberry significantly reduced the odds of UTI manifestation in the studied children compared to placebo (OR=0.31; 95% CI: 0.21 to 0.46;  $p<0.0001$ ). On the other hand, it was determined that effectiveness of cranberry in decreasing UTI manifestation was similar to antibiotic treatment (OR=0.75; 95% CI: 0.34 to 1.70;  $p=0.495$ ) (**Figure.3**).

### 3-4. Prevalence of UTI in children under treatment with cranberry and placebo

Prevalence of UTI in children under treatment with cranberry was calculated to be 0.26 (95% CI: 0.22 to 0.30), while it was 0.49 (95% CI: 0.44 to 0.53) in the placebo group. Additionally, in studies that had used antibiotics as the strategy for control group, the prevalence of UTI in cranberry group was 0.11 (95% CI: 0.05 to 0.18), which did not differ from its prevalence of 0.14 (95% CI: 0.09 to 0.20) in the group under treatment with antibiotics (**Figure.4**).

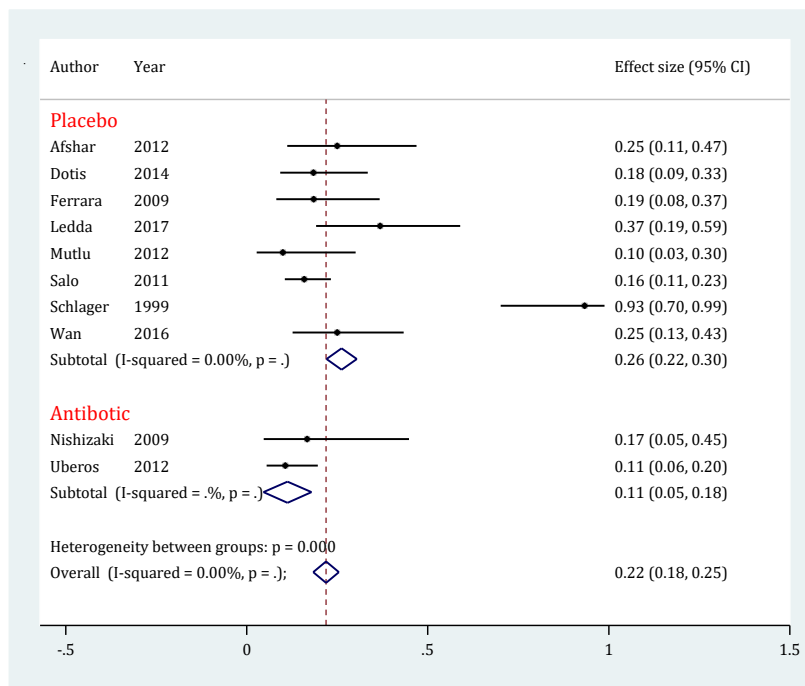


**Fig.2:** Assessment of risk of bias (A) and publication bias (B).

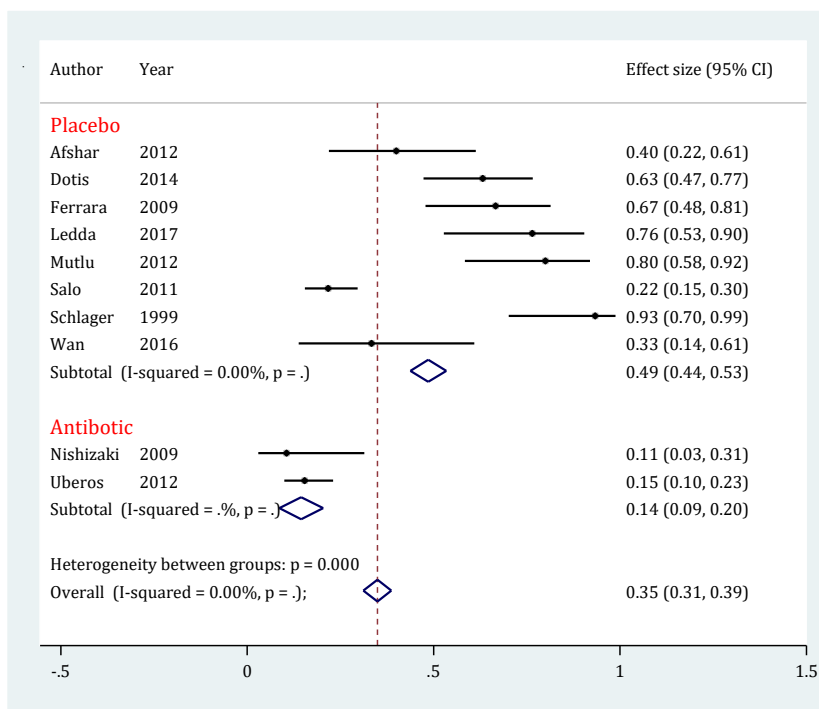


**Fig.3:** Pooled odds ratio (OR) of urinary tract infection after treatment by cranberry extract compared to placebo and antibiotic prescription. CI: Confidence interval.

**A**



**B**



**Fig.4:** Prevalence (effect size) of urinary tract infection in cranberry treated (A) and control (B) groups. Analyses were stratified according to control group strategy (placebo or antibiotic therapy). CI: Confidence interval.

#### 4- DISCUSSION

The present systematic review and meta-analysis showed that consumption of cranberry extract can significantly reduce UTI manifestation in children. This effectiveness is comparable to antibiotic treatment. In comparison to the findings of this study, Dessi et al. carried out a systematic review in 2011 and showed that 7 out of the 9 included studies indicated that cranberry extract consumption leads to prevention of UTI manifestation in children (19). In another systematic review in 2015 Durham et al. evaluated 8 studies and expressed that prescription of cranberry can prevent manifestation of UTI in healthy children (10).

However, Jepson et al. included 2 articles in their meta-analysis and showed that cranberry extract consumption does not have an effect on UTI manifestation in children (20). As can be seen, Dessi et al. and Durham et al. studies lack meta-analysis and have reached a conclusion qualitatively. In addition inclusion of only 2 articles in Jepson et al. study has yielded results that contradict the findings of the present meta-analysis. In addition, the 2 systematic reviews by Dessi et al. and Durham et al. had also included retrospective studies, which is an important weak point for these studies. In the present study, by including 10 clinical trials and with a meta-analysis approach, efforts were made to eliminate the limitations of the previous systematic reviews.

Analyses showed that consumption of cranberry extract could reduce manifestation of UTI up to about 50% compared to placebo group. This rate is considerable and can significantly reduce the burden of the disease. Meanwhile, researches show that UTI incidence has increased in recent years and the financial and treatment costs caused by this disease are also rapidly rising (28). Therefore,

using the strategy of prophylaxis with cranberry can be helpful in this regard. Moreover, in the included studies, practically no side effects have been reported for cranberry extract, which indicates the safety of this natural compound. Yet, consumption of antibiotics has always been associated with the risk of manifesting undesirable side effects. One of the strong points of the present study was the extensive search in databases and obtaining the maximum number of articles available in the field of evaluating the effectiveness of cranberry in prevention of UTI manifestation in children.

This resulted in lack of publication bias in the study as well as absence of heterogeneity regarding evaluation of UTI prevalence. Nevertheless, the present study also had limitations. The first limitation was that applying various treatment protocols for prescription of cranberry in the articles prevented us from finding the best duration of prescription for this extract, its best dose and the most proper treatment period for this prophylaxis. Furthermore, duration of follow-up varied from 2 to 17 months between the studies, which is another limitation of the present meta-analysis since follow-up period is one of the factors that might cause heterogeneity between the studies.

Yet, due to the small number of studies subgroup analysis could not be done. Finally, it should be noted that 8 of the 10 studies included had been carried out in developed countries and the remaining 2 were performed on children in Turkey and Taiwan. Therefore, considering the difference in bacterial pattern of UTI in developed and developing countries, generalizing these results to developing countries can be a little difficult.

#### 5- CONCLUSIONS

In the present study, by using a meta-analytic approach, it was determined that



consumption of cranberry extract leads to children and its effectiveness is similar to that of antibiotics. However, it is not yet known what the best treatment protocol, dose, and duration of cranberry extract prescription are for prevention of UTI in children. Therefore, it is suggested that future clinical trials look to introduce the best treatment protocol for cranberry in prevention of UTI.

## 6- CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

## 7- ACKNOWLEDGMENTS

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





























































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**Table-1:** Characteristics of included studies

Author, Year, Country	Design	Age	Gender*	Control/treated#	Treatment strategy	Control group	Diagnosis of UTI	Follow up (month)
Afshar, 2012, Canada (21)	Parallel	5 to 18	39	20 / 20	Daily for 12 months; 2 ml/kg	Placebo	Positive urine cultures	12
Dotis, 2014, Greek (9)	Parallel	2 to 18	53	38 / 38	Daily for at least 3 months; 2 capsule	Placebo	Positive urine cultures	12
Ferrara, 2009, Italy (11)	Parallel	3 to 14	84	27 / 27	Daily for 6 months; 50 ml	Placebo	Positive urine cultures	6
Ledda, 2017, Italy (22)	Parallel	12 to 18	19	17 / 19	Daily for 2 months; 1capsule	Placebo	Positive urine cultures	2
Mutlu, 2012, Turkey (23)	Cross over	4 to 18	26	20 / 20	Daily for 6 months; 1capsule	Placebo	Positive urine cultures	6
Nishizaki, 2009, Japan (24)	Parallel	0 to 2.5	13	19 / 12	Daily for 17 months; 100 ml	Antibiotics	Positive urine cultures	17
Salo, 2011, Finland (25)	Parallel	1 to 16	232	129 / 126	Daily for 6 months; 5 ml/kg	Placebo	Positive urine cultures	12
Schlager, 1999, US (26)	Cross over	2 to 18	16	15 / 15	Daily for 3 months; 300 ml	Placebo	Positive urine cultures	6
Uberos, 2012, Spain (27)	Parallel	0 to 13	112	117 / 75	Daily for 12 months; 0.2 ml/kg	Antibiotics	Positive urine cultures	12
Wan, 2016, Taiwan (18)	Parallel	6 to 18	0	12 / 28	Daily for 6 months; 120 ml	Placebo	Positive urine cultures	6

\*, Number of female patients, #, Sample size (n).

**Table-2:** Quality assessment of eligible studies

	Afshar, 2012	Dotis, 2014	Ferrara, 2009	Ledda, 2017	Mutlu, 2012	Nishizaki, 2009	Salo, 2011	Schlager, 1999	Uberos, 2012	Wan, 2016
 Low risk										
 Unclear										
 High risk										
Random sequence generation										
Allocation concealment										
Blinding of patients and researchers										
Blinding of outcome assessment										
Incomplete outcome data										
Selective reporting										
Other bias	