A Clinical Trial of Cranberry and Elderberry Extracts (Berdi® Sachet) for Urinary Tract Infection in Pakistani Population

Yasir Mehmood\textsuperscript{1*}, Hafiz Umar\textsuperscript{2}, Humayun Riaz\textsuperscript{1}, Umar Farooq\textsuperscript{1} and Hammad Yousaf\textsuperscript{1}

\textsuperscript{1}Rashid Latif College of Pharmacy, Lahore, Pakistan.
\textsuperscript{2}Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan.

Authors’ contributions
This work was carried out in collaboration among all authors. Author YM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors HY and HU managed the analyses of the study. Authors HR and UF managed the literature searches. All authors read and approved the final manuscript.

Article Information
DOI: 10.9734/JPRI/2019/v31i630347

Received 28 September 2019
Accepted 02 December 2019
Published 09 December 2019

ABSTRACT

Lower urinary tract infection (UTI) is very common diseases. Recurrent UTI remain challenging to treat because the main treatment option is long-term antibiotic and this poses a risk for the emergence of bacterial resistance. Some options to avoid this risk are available, including the use of cranberry and elderberry products (herbal products extract). However, this can lead to the advent of bacterial resistance. The cross sectional study was designed to evaluated the efficacy of above products. The study was conducted from 23 October 2019 to 28 October 2019 in Arif Memorial Teaching Hospital, Lahore, Pakistan. The subjects were outpatients aged 20 to 65 years. UTI symptoms were recorded in the daily diary before, during and after treatment and assessed by the Jackson score. Following approval by the Ethics Committee of Rashid Latif Pharmacy College, the questionnaire (ROUTE2-002) was compiled and information of UTI patients using cranberry and elderberry extracts (Berdi® Sachet) was collected. Compliance and tolerability were
considerable obstacles in this study. A total of 67 patients were screened for participation; 12 were unwilling to participate and 55 were enrolled for clinical trial and all patients had urinary tract irritation. In this study 55 (100%) UTI patients were cured with cranberry and elderberry extracts (Berdi® Sachet). Further investigation is needed to confirm this effect and to evaluate the health benefits of cranberries and elderberry.

**Keywords:** Urinary tract infection; cranberry; symptoms; cure.

1. **INTRODUCTION**

Low urinary tract infections (UTI) are very common and it is estimated that at least 60% of women suffering at some stages in their lives [1-3]. Due to the universality of UTI, it is a public health problem with an estimated cost of more than $ 25 billion for diagnosis and treatment over a 20-year period (approximately $ 2.47 billion in 2000) [1,4]. Urinary tract infections in adult women are about 50 times higher than in men, as women have a shorter urethra and bacteria can go up into the bladder. Colonization of the peri-urethral tissues is the first step of infection followed by bacterial passage through the urethra. The second step is the proliferation of bacteria on the urethra and bladder wall [5,6]. Urinary tract infections are caused by Gram-negative bacteria. In fact, E. coli accounts for most cases [2,3,5,7]. Antibiotic is the first choice of treatment and recurrence is alarming sign [7]. Risk factors for women with urinary tract infections include sexual intercourse, contraceptives, antibiotic resistance, menopause, genetics and bacterial virulence [2].

Cranberry is an abbreviation of "Herb berry". The name derives from the nickname of the blueberry blossom [8]. Cranberry belongs to the **Ericaceae** family and grows naturally in peat-stained sour swamps filled with moist forests [9]. The cranberry (**Vaccinium macrocarpon**) has been used in the past by North American Indians to treat urinary tract infections [8]. Other relatives of the cranberry family (European Cranberry - **Oxycoccus**, Blueberry - **V. vitisidaea**, Blueberry - **V. myrtillus**) have some of the basic ingredients of cranberry, but there are few research findings that support prevention [10,11]. Cranberry consists of water (88%), organic acids (including salicylates), fructose, vitamin C (high content, i.e. 200 mg / kg fresh berries), flavonoids, anthocyanins, catechins and triterpenoids compound [8]. Anthocyanins and proanthocyanidins (PAC) are tannins (stable polyphenols) which have a natural defense against microorganisms [8,12].

Usual preparations for cranberries are fresh whole berries, gelatinized products, juice (usually 10-25% pure juice), sachets and capsules. Even with sweeteners, pure juice is also acidic (pH, 2.5) and too inedible [8].

In recent years, elderberry has gained popularity among researchers and the broader community through its antioxidants, antidiabetics, anti-inflammatory and immunomodulatory agents and its antidepressant properties. The berries are dark purple black stone fruits that grow in clusters and whose color is attributed to anthocyanins. A group of phenolic compounds in flavonoids is rich in elderberries and is considered an active ingredient of fruits. Nevertheless, elderberry also comprises a number of nutrients, including vitamins (A, B1, B2, B6, B9, C and E), trace elements (e.g., Cu, Zn, Fe, and minerals (eg, K, Ca, and Mg) and phytochemicals), Carotenoids, plant sterols and polyphenols. The elderberry becomes an important candidate for not only respiratory tract, but also for cardiovascular and mental health, for due to the presence of these additional ingredients.

1.1 **Mechanism of Action**

E. coli has important property of adherence to host. Pili or fimbriae is the adherence protein [3]. The cell surface of Pili or fimbriae has exposed lectins that bind to host carbohydrate. Pili are short filamentous structure that help bacteria to bind to host tissue, pili are proteinaceous structure that maybe mannose-resistant or sensitive. P-fimbriae is more contagious strain of E. coli that is isolated from patients suffering from recurrent UTI and pyelonephritis. The p-fimbriae binds to glycosphingolipids in the lipid bilayer of renal cells [6]. Cranberries contain two compounds with antiadherence properties that prevent fimbriated Escherichia coli from adhering to uroepithelial cells in the urinary tract. Approximately one dozen clinical trials have been performed testing the effects of cranberries on the urinary tract. However, these trials suffer from a number of limitations. Most importantly,
the trials have used a wide variety of cranberry products, such as cranberry juice concentrate, cranberry juice cocktail, and cranberry capsules, and they have used different dosing regimens. This study focused on cranberry and elderberry extract in sachet form (Berdi® Sachet).

2. MATERIALS AND METHODS

This cross-sectional study included 55 patients less than age 65 years (median age: 27 years, range 20-65) that were treated with Berdi® Sachet for UTI and related symptoms. These patients were initially weakened due to UTI (100%) and nobody was taking medicine (100%). The effects of Berdi® Sachet was evaluated at 5th day after intake with visual analog scales for pain, irritation, strong and frequent urge to urinate, cloudy, bloody, or strong-smelling urine and burning sensation. ROUTE2-002 questionnaire was developed to collect information. Adverse effects of Berdi® Sachet (nausea, vomiting, headache and abdominal pain) were also evaluated. The data were analyzed with Microsoft excel.

2.1 Study Design

A questionnaire based study was conducted based on a self-administered questionnaire; study was conducted at local hospitals for a period of seven days 23-10-2019 to 28-10-2019.

2.2 Sampling and Sample Size

The sample size was estimated by using Krejcie and Morgan’s sample size calculator (Krejcie RV and Morgan DW, 1970). A suitability sampling technique was used to recruit a sample of 55 participants from residents of Pakistan.

2.3 Survey Instrument

A questionnaire (ROUTE2-002) was used to assess the treatment outcomes or cure after the use of Berdi® Sachet. The questionnaire contains three sections. The first section contained items related to sign and symptoms before cure. The second section contains treatment outcomes after the exposure of Berdi® Sachet. The last portion of questionnaire contained the information about the adverse effect after the exposure of Berdi® Sachet. Questionnaire was in local and English language and was designed by assistant professor Rashid Latif College of Pharmacy (RLCP).

2.4 Materials Used in the Study

Cranberry and elderberry extracts (Berdi® Sachet. Dose (2 sachets each day).

2.5 Inclusion and Exclusion Criteria

The following inclusion criteria were used for the selection of patients.

(a) Age ≤ 65 years.
(b) UTI symptoms.
(c) Patients don’t take any medicine.
(d) Do not have consumed cranberry juice, polyphenols or antioxidant supplements in the last 2 weeks.

The following exclusion criteria were used for the selection of patients:

(a) Have an indwelling bladder catheter in place.
(b) Patients having sever viral problems.
(c) Patients already talking medicines.
(d) Patients with a history of nephrolithiasis because cranberry may increase the risk of nephrolithiasis.

3. RESULTS

3.1 Patient Characteristics

A total of 67 patients were screened for participation; 12 were unwilling to participate and 55 were enrolled for clinical trial and all patients had urinary tract irritation. 10 patients had a negative urine culture result but they felt severe irritation in urinary tract. The remaining 45 eligible had positive urine culture. The mean patient age was 27 years, Almost all (99%) patients had a history of >1 UTI. The most common organisms isolated from the index and recurring UTI were E. coli. The majority were students, and less than 10% were married or living as married.

3.2 Outcome Associated with Treatment

Urinary tract infection is most common infection especially in women. The use of allopathic drugs has been considered as one of the effective treatment. But this is not feasible as besides being most cost prohibitive, they are not without side effects. For this purpose a coded herbal formulation (Berdi® Sachet) has been formulated. It contains the cranberry and
elderberry powder, which is known for its wide range of clinical use in indigenous medicine. In our clinical trial for we observed patients suffered with pain, irritation, strong and frequent urge to urinate, cloudy, bloody or strong-smelling urine and burning sensation which is indication of UTI. We tried to cure UTI and related symptoms with (Berdi® Sachet). Berdi® Sachet has been found effective in UTI patients. 5th day follow-up questionnaires, gastrointestinal symptoms were reported twice as frequently for those receiving cranberry and elderberry extract (Berdi® Sachet). There were no serious adverse events occurred in all cured patients and none were deemed to be attributable to treatment after review by the data safety monitor.

3.3 Treatment response at 5th day

In this study, we administered (Berdi® Sachet) to patients with UTI symptoms and collected information. Out of 55 patients, 19 were male and 36 were females. All patients had submitted questionnaire to project administrator. Sign and symptoms of UTI were observed and not down before treatment and mentioned in Table 1. Treatment time line was decided 5th day and most of patients were cured after 5th day. Irritation was 95.12% cured after 5th day of treatment. Burning 100%, abdominal pain 89.65%, smelling urine 96.6% and bloody urine (hematuria) 75% were cured.

3.4 Adverse Effect

There is no severe adverse effect reported in previous preclinical studies of cranberry and elderberry. In our study twenty one (21.8%) of the patients had gastrointestinal upsets, including nausea, vomiting, and diarrhea, and dislike of the taste. Although high rates of gastrointestinal upset (more than 10%) were reported in some studies the rates of adverse events with gastrointestinal upset were relatively low in other studies. One subject reported adverse effect gastrointestinal upset but it was not included because at the same he has ulcer complications.

Table 1. Patient profile and characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Average)</td>
<td>27±2.1</td>
</tr>
<tr>
<td>Gender</td>
<td>20-65</td>
</tr>
<tr>
<td>Male</td>
<td>19 (34.54)</td>
</tr>
<tr>
<td>Female</td>
<td>35 (65.45)</td>
</tr>
<tr>
<td>Symptoms before treatment</td>
<td></td>
</tr>
<tr>
<td>Irritation</td>
<td>41 (74.54)</td>
</tr>
<tr>
<td>Burning</td>
<td>45 (81.81)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>29 (52.72)</td>
</tr>
<tr>
<td>Strong-smelling urine</td>
<td>30 (54.54)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>08 (14.54)</td>
</tr>
</tbody>
</table>

Table 2. Therapy efficacy and safety characteristics

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of disease</td>
<td>UTI</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>5 days</td>
</tr>
<tr>
<td>Status n (% Cured) after 5th day</td>
<td></td>
</tr>
<tr>
<td>Irritation</td>
<td>02 (95.12)</td>
</tr>
<tr>
<td>Burning</td>
<td>0 (100)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>03 (89.65)</td>
</tr>
<tr>
<td>Smelling urine</td>
<td>01 (96.6)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>02 (75)</td>
</tr>
</tbody>
</table>

Fig. 1. Symptoms before treatment
4. DISCUSSION

Urinary tract infection (UTI) is the most common infection in population throughout the world. The primary aim of this study was to test the efficacy of cranberry and elderberry extracts (Berdi® Sachet) in the reduction of UTI and related symptoms. In this study the number of participants was relatively small but those participants provided enough information. Although antibiotics may have an advantage over cranberry and elderberry products for the treatment and prevention of UTI but adverse events can occur and the development of resistant microorganisms is inevitable. Cranberry and elderberry products however never induce antibiotic-resistant bacteria or lose their efficacy. Of note, intravaginal estriol, vaginal suppositories of a probiotic and intravesical administration of hyaluronic acid have been evaluated to clarify their efficacies for the prevention of UTI and they induced no resistant microorganisms. However, there is one known unfavorable factor in cranberry and elderberry extract that is the tolerability of consuming cranberry and elderberry products during a somewhat long period. Cranberries and elderberry are clinically significant in various conditions and have been tested [3,7,12,13]. Various studies are conducted on cranberries and elderberry due to their use in UTI prophylaxis in female, males and children. The studies have also been conducted on their use in neurogenic bladder and pregnancy [10]. A pilot clinical trial with elderberry and cranberry extract sachet confirmed a beneficial effect on severity of UTI symptoms. In this clinical trial the possible beneficial effects of supplements (Berdi® sachet) in UTI were examined. We conducted a cross sectional study trial to determine the effectiveness of elderberry and cranberry extract in UTI patients and found results were significant.

5. CONCLUSION

The finding from this clinical trial demonstrated there were statistically significant results of herbal extract (Berdi® sachet) against UTI and its associated symptoms. Hence, (Berdi® sachet) possesses a therapeutic value for the treatment of UTI and its associated symptoms. However, further clinical trials on larger scale and studies pertaining to mechanism of action of (Berdi® sachet) are suggested.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

This study was endorsed by Ethics Committee of RLCP, Lahore Pakistan and was carried in acquiescence with the Helsinki Declaration. The need for informed consent was renounced because of the study design.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


© 2019 Mehmood et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com review-history/53027