

22 **Introduction:**

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

35 Cranberry is an abbreviation of "Herb berry". The name derives from the nickname of the
36 blueberry blossom, which looks like the head of the sandbar at the withers. It usually feeds on
37 the berries of this plant [8]. Cranberry belongs to the Ericaceae family and grows naturally in
38 peat-stained sour swamps filled with moist forests [9]. The cranberry (*Vaccinium macrocarpon*)
39 has been used in the past by North American Indians to treat urinary tract infections [8]. Other
40 relatives of the cranberry family (European Cranberry - *Oxycoccus*, Blueberry - *V. vitisidaea*,
41 Blueberry - *V. myrtillus*) have some of the basic ingredients of cranberry, but there are few
42 research findings that support prevention [10, 11]. Cranberry consists of water (88%), organic
43 acids (including salicylates), fructose, vitamin C (high content, ie 200 mg / kg fresh berries),
44 flavonoids, anthocyanins, catechins and triterpenoids compound [8]. The chemical ingredient
45 responsible for the taste is the irisoside. Anthocyanins and proanthocyanidins (PAC) are tannins
46 (stable polyphenols) that are found only in vaccinia berries and have a natural defense against
47 microorganisms [8, 12].

48 Usual preparations for cranberries are fresh whole berries, gelatinized products, juice (usually
49 10-25% pure juice), sachets and capsules. Even with sweeteners, pure juice is also acidic (pH,
50 2.5) and too inedible [8].

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

61 **Mechanism of action**

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

75 **Material and Method**

76 This cross sectional study included 55 patients less than age 65 years (median age: 27 years,
77 range 20 - 65) that were treated with *Berdi® Sachet* for UTI and related symptoms. These
78 patients were initially weakened due to UTI (100%) and nobody was taking medicine (100%).
79 The effects of *Berdi® Sachet* was evaluated at 5th day after intake with visual analog scales for
80 pain, irritation, strong and frequent urge to urinate, cloudy, bloody, or strong-smelling urine and

81 burning sensation. ROUTE2-002 questionnaire was developed to collect information. Adverse
82 effects of *Berdi® Sachet* (nausea, vomiting, headache and abdominal pain) were also evaluated.
83 The data were analyzed with Microsoft excel.

84 **Study design**

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

87 **Sampling and sample size**

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

91

92 **Survey instrument**

93 The survey questionnaire used to assess the treatment outcomes or cure after the use of *Berdi®*
94 *Sachet*. The questionnaire contains three sections. The first section contained of items related to
95 sign and symptoms before cure. The second section contains treatment outcomes after the
96 exposure of *Berdi® Sachet*. The last portion of questionnaire contains the information about the
97 adverse effect after the exposure of *Berdi® Sachet*. Questionnaire was in local and English
98 language and was designed by assistant professor (RLCP)

99 **Materials used in the study**

100 *cranberry and elderberry extracts (Berdi® Sachet)*

101 **Inclusion and exclusion criteria**

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

103 (a) Age \geq 65 years.

104 (b) UTI symptoms.

105 (c) Patients don't take any medicine.

106 (d) Do not have consumed cranberry juice, polyphenols or antioxidant supplements in the last 2
107 weeks.

108

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

110 (a) Have an indwelling bladder catheter in place.

111 (b) Patients having severed viral problems.

112 (c) Patients already taking medicines.

113 (d) Patients with a history of nephrolithiasis because cranberry may increase the risk of
114 nephrolithiasis.

115 **Ethical standard**

116 This study was endorsed by Ethics Committee of Rashid Lateef Medical and Pharmacy College
117 and Hospital Lahore Pakistan and was carried in acquiescence with the Helsinki Declaration. The
118 need for informed consent was renounced because of the study design.

119 **Results**

120 **Patient Characteristics**

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

128 **Outcome Associated with Treatment**

129 We observed pain, irritation, strong and frequent urge to urinate, cloudy, bloody, or strong-
130 smelling urine and burning sensation. Overall, the recurrence rate was 16.9%, lower than the
131 expected 30. The presence of UTI symptoms at 5th day was almost similar, with overall no
132 marked differences. 7th day follow-up questionnaires, gastrointestinal symptoms were reported
133 twice as frequently for those receiving cranberry and elderberry extract (Berdi® Sachet). There
134 were no serious adverse events occurred in all cured patients and none were deemed to be
135 attributable to treatment after review by the data safety monitor.

136

137

138 **Treatment response at 5th day**

139 In this study, we administered (Berdi® Sachet) to patients with UTI symptoms and collected
140 information. Out of 55 patients, 19 were male and 36 were females. All patients had submitted
141 questionnaire to project administrator. Sign and symptoms of UTI was observed and not down
142 before treatment and mentioned in table 1. Treatment time line was decided 5 days and most of
143 patients were cured after 5th day. Runny nose and sneezing was 100% cured after 3rd day of
144 treatment. Temperature 90.2%, sore throat 83.05%, lethargy 88% and headache 79.245 were
145 cured. Rest of patients was cured after 7th day of treatment.

146 **Adverse Effect.**

147 There are no severe adverse effect reported in previous clinical studies but in one study, in
148 pregnant women 73 (38.8 %) of 188 participants could not complete the course and withdrew.
149 Forty-four (60.3 %) of the 73 women had gastrointestinal upsets, including nausea, vomiting,
150 and diarrhea, and dislike of the taste. Although high rates of gastrointestinal upset (more than 10
151 %) were reported in some studies the rates of adverse events with gastrointestinal upset were
152 relatively low in other studies.

153 In our trials there were no specified symptoms of adverse effect. Subjects did not report specific
154 symptoms including gastrointestinal upset, nausea and diarrhea. One subject reported adverse
155 effect gastrointestinal upset but it was not included because at the same he has ulcer
156 complications. One more subject had reported dizziness and itchy skin and after one day he
157 became normal. As strict principles were undertaken, only few cases of adverse events were
158 reported as shown in table 3.

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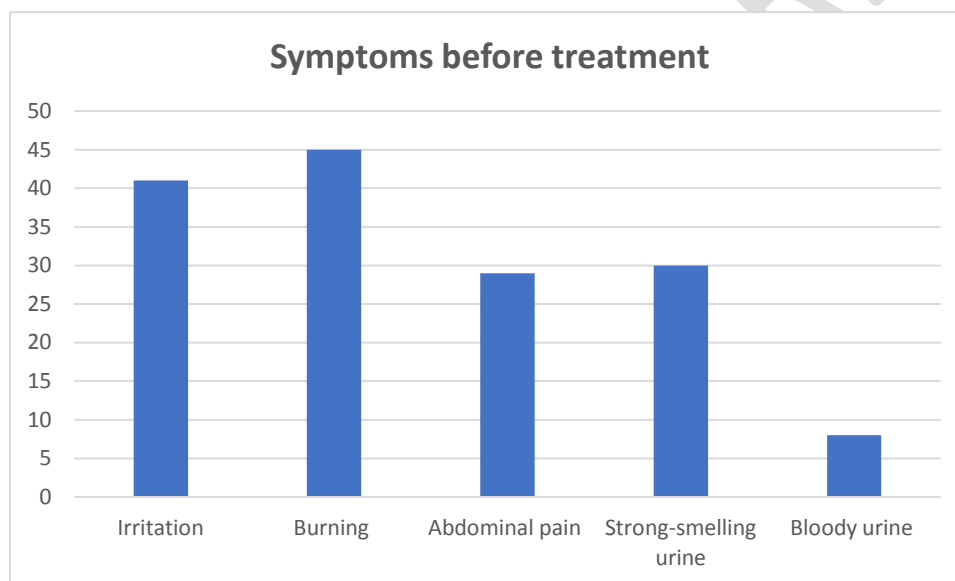
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Table 1 Patient profile and characteristics	
Characteristic	n (%)
Age in years (Average)	
Mean \pmSD	27\pm2. 1

Range	20-65
Gender	
Male	19 (34.54)
Female	35 (65.45)
Symptoms before treatment	
Irritation	41 (74.54)
Burning	45 (81.81)
Abdominal pain	29 (52.72)
Strong-smelling urine	30 (54.54)
Bloody urine	08 (14.54)

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163 Fig. 1 Symptoms before treatment



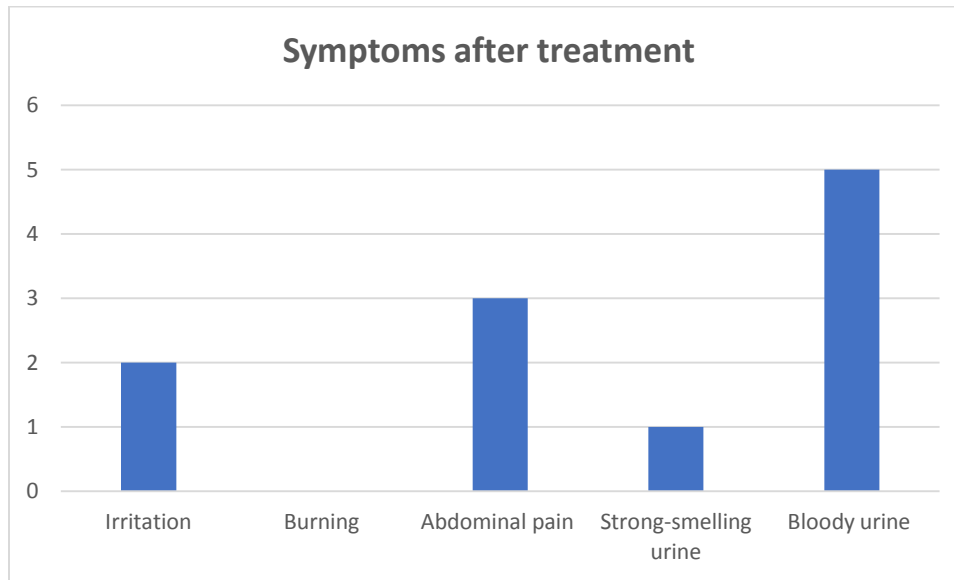
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Table 2 Therapy efficacy and safety characteristics	
Patients characteristics	
Type of disease	UTI
Duration of treatment	5 days
Status n (%) after 5 days	
Irritation	02 (95.12)

Burning	0 (100)
Abdominal pain	03 (89.65)
Strong-smelling urine	01 (96.6)
Bloody urine	05 (37.5)

165

166 Fig. 2 Symptoms after treatment



167

168 Discussion

169 Urinary tract infection (UTI) is the most common infection in population throughout the world.
 170 The primary aim of this study was to test the efficacy of cranberry and elderberry extracts
 171 (Berdi® Sachet) in the reduction of UTI. In this study the number of participants was relatively
 172 small but those participants provided enough information.

173 Although antibiotics may have an advantage over cranberry products for the treatment and
 174 prevention of UTI but adverse events can occur and the development of resistant microorganisms
 175 is inevitable. Cranberry products, however never induce antibiotic-resistant bacteria or lose their
 176 efficacy. Of note, intravaginal estriol, vaginal suppositories of a probiotic and intravesical
 177 administration of hyaluronic acid have been evaluated to clarify their efficacies for the
 178 prevention of UTI and they induced no resistant microorganisms. However, there is one known
 179 unfavorable factor in cranberry and elderberry extract that is the tolerability of consuming

180 cranberry and elderberry products during a somewhat long period. Cranberries and elderberry are
181 clinically significant in various conditions and have been tested [3, 7, 12, 13]. Various studies are
182 conducted on cranberries and elderberry due to their use in UTI prophylaxis in female, males and
183 children. The studies have also been conducted on their use in neurogenic bladder and pregnancy
184 [10].A pilot clinical trial with elderberry and cranberry extract sachet confirmed a beneficial
185 effect on severity of urinary tract infections symptoms. In this clinical trial the possible
186 beneficial effects of supplements (Beri® sachet) in UTIs were examined. We conducted a cross
187 sectional study trial to determine the effectiveness of elderberry and cranberry extract in UTI
188 patients.

189

190 **COMPETING INTERESTS DISCLAIMER:**

191

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

198

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