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Effect of Aqueous Cranberry (*Vaccinium arctostaphylos* L.) Extract Accompanied with Antibiotics on Urinary Tract Infections caused by *Escherichia coli in vitro*

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The chemical compositions of the different species of Cranberry were studied widely. In the most species of Cranberry some chemical compounds such as Flavonoids, sugar, protein, total fat and some important fatty acids were identified. Urinary tract infections (UTI) are common in women and children and they cause some permanent side effects on kidneys. Since many years, people for treatment of UTI, utilize this herb with or without appropriate antibiotics. In this study, the synergistic and/or antagonistic effect of aqueous Cranberry (*Vaccinium arctostaphylos L.*) extract accompanied with antibiotics (Ciprofloxacin, Amikacin, Ampicillin and Nitrofurantoin) was carried out on UTIs caused by *Escherichia coli in vitro*. The results show that because of suppression of the appropriate medicinal effect of antibiotics by *Vaccinium arctostaphylos* it is better not to use this medicinal herb for treating UTIs with the antibiotics.

Key words: *Vaccinium arctostaphylos* L., Urinary tract infections, Antibiotics, *Escherichia coli*.

Vaccinium genus that is relevant to the *Ericaceae* family has over 450 species which are found mostly in the cooler areas. *Vaccinium arctostaphylos* a deciduous shrub grows 2-3m. It is in flower from May to July, and the seeds ripen in September. The flowers are hermaphrodite and are pollinated by insects[1]. The plant prefers well drained light (sandy) and medium (loamy) soils. It prefers acidic soils and can tolerate very acid soil (pH 4-5). It can grow in semi-shade (light woodland) or no shade. It requires moist soil[1]. This kind of Cranberry (*V. arctostaphylos*) is growing in north and the parts of west of Iran. The local name of this herb is *Qare-Qat* (QΛre-QΛt).

The main chemical components that were extracted from Cranberry contained mineral compounds, flavonoids, benzoic acid, triterpenoids, anthocyanins, catechin, β-hydroxybutiric acid,citric acid, glucuronic acid, quinic acids, ellagic acid, sugar(fructose, *D*-mannose), protein, total fat and some important fatty acids. In one study, the chemical composition of *V. arctostaphylos* essential oil was determined

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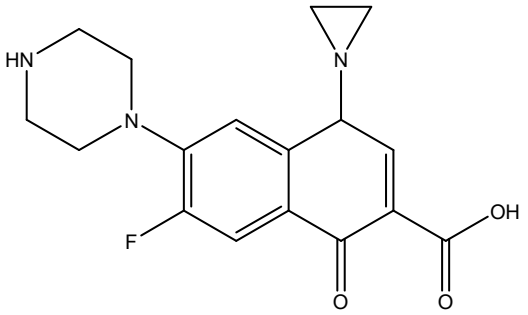
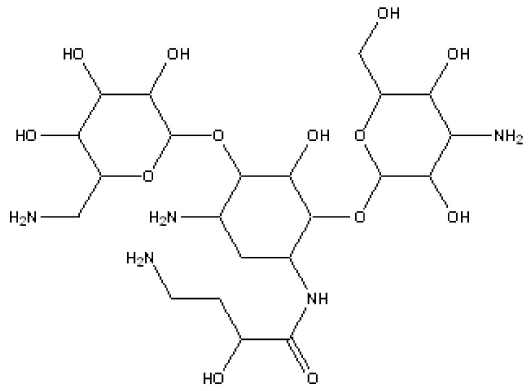
by employing GC and GC/MS methods[2]. The major determined volatiles in this type of Cranberry, are: hexadecanoic acid(27%), vitispirane(6.5%), β-ionone (5.9%) and sandaracopimaradiene(4.8%)[2]. Foo *et al.* in (2000) reported the proanthocyanidin fraction of Cranberry, isolated from the ethyl acetate extract that was investigated for ability to prevent adherence of *E. coli* to mannose-resistance adhesion by determining the ability to prevent agglutination of both isolated P-receptor resin-coated beads and human erythrocytes[3]. The characterization of Flavonols in Cranberry (*Vaccinium macrocarpon*) were investigated by Vorsa *et al.*[4]. In this report, the main Flavonols were extracted by acetone and ethylacetate and identified in this herb, such as: myricetin-3-β-xylopyranoside, quercetin-3-β-galactoside, quercetin-3-β-glucoside, quercetin-3-α-arabinopyranoside, quercetin-3-α-arabinofuranoside, 3'-methoxyquercetin-3-α-xylopyranoside, quercetin-3-O-(6''-p-coumaroyl) β-galactoside and quercetin-3-O-(6''-benzoyl)α-galactoside[4].

In a survey carried out in 1984, the anti adhering of Cranberry on 77 strains of *E. coli* in 75% samples was verified[5]. In another investigation, the extract of this herb was tested for treating 153 persons who suffered from UTIs[6]. In 1995, it was showed that UTI in women is decreased to 52% by Cranberry extract prophylaxis[7-8]. In 2006, the effect of Cranberry in prevention of urinary tract infection in children, and prevention of nonspecific bacterial cell adhesion in immunoassays was probed by use of Cranberry juice[9,10]. Sometimes people for treatment of UTIs, utilize this herb with appropriate antibiotics.

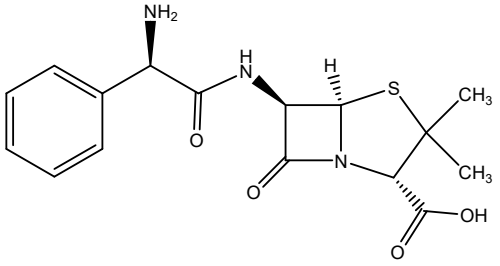
In this study, the interference and/or synergistic effect of aqueous Cranberry (*Vaccinium arctostaphylos*) extract accompanied with antibiotics (Ciprofloxacin-1, Amikacin-2, Ampicillin-3 and Nitrofurantoin-4) was investigated on isolates of *Escherichia coli* cause UTI, *in vitro*.



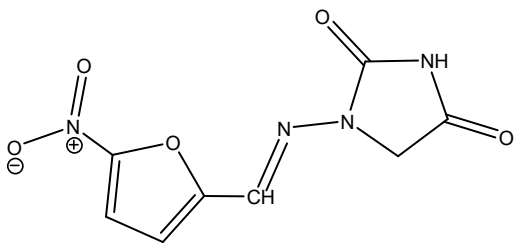
Ciprofloxacin(1)



Amikacin (2)



Amipicillin (3)



Nitrofurantion(4)

Fig. 1. The chemical structures of Ciprofloxacin-**1**, Amikacin-**2**, Ampicillin-**3** and Nitrofurantoin-**4**

EXPERIMENTAL

In this study, 61 isolates of *E. coli* from urine samples of the patients referred to hospitals and laboratories of Sanandaj city were examined. Dried fruit of Cranberry (*Vaccinium arctostaphylos*) were powdered and then subjected to aqueous extraction (1%). This concentration was based on Boland's study. The maximum concentration of Cranberry in media was selected that had no effect on bacteria on the media than media without plant extract. One control plate (Mueller-Hinton agar without Cranberry) was chosen for each strain. The other plate contained Mueller-Hinton agar accompanied Cranberry 1% extract. A certain number of bacteria ($1.5x10^8$ CFU/ml) based on 0.5 Macfarland scale were cultured on the media. After this stage, the culture was tested with antibiotic disks (Ciprofloxacin-1, Amikacin-2, Ampicillin-3, Tetracyclin, Co-trimoxazole, Nalidixic acid, Ceftazidime and Nitrofurantoin-4). After 24 hours of incubation at 37°C the zone of inhibition was measured around each disk and compared with standard schedule[11].

RESULTS AND DISCUSSION

The results of the investigation are demonstrated in Table 1. The results were analyzed based on Ki test. The most susceptibility belonged to Amikacin-2 in frequency of the control group with 93.45%. The lowest frequency was 9.8% for Ampicillin-3. The other type of antibiotics the susceptibilities in control group were: Co-trimoxazol 39.34%, Ceftazidime 51%, Nalidixic acid 54.1%, Nitrofurantoin 62.3%, Tetracyclin 72.13% and Ciprofloxacin-1 73.8%. In test group, Nitrofurantoin-4 shows the most susceptibility (72.13%) and the lowest belonged to Ampicilline(18%). In addition, percentage of susceptibility for other antibiotics such as Amikacin, Co-trimoxazole, Nalidix acid, Ceftazidime and Tetracyclin were: 28.87%, 34.42%, 52.48%, 55% and 70.5%, respectively.

In accordance with the results, not only aqueous extract of Cranberry showed no synergistic effect with any antibiotics, but also it showed severe antagonistic effect against Ciprofloxacin-1 and Amikacin-2 (P=0.00).

Table 1. The comparison of the sensitivity of *Escherichia coli* to the antibiotics ± Cranberry (1-4).

Concerns		Ciprofloxacin(1)			Amikacin(2)			Ampicillin(3)			Nitrofurantoin(4)		
		Blank*	Cranberry**	Total	Blank	Cranberry	Total	Blank	Cranberry	Total	Blank	Cranberry	Total
Susceptibility	No.	45	11	56	57	17	74	6	11	17	38	44	82
	%	73.8	18	-	93.45	28.87	-	9.8	18	-	62.3	72.13	-
Stability	No	16	50	66	4	44	48	55	50	105	23	17	40
	%	26.2	82	-	6.55	72.13	-	90.2	82	-	73.7	27.87	-

The P-value for the samples was 0.00
* Black - Control plate; ** Cranberry - test plate

(Table 1). However, in acidic pH Ampicillin-3 and Nitrofurantoin-4 had 10% increase in function, but on the whole, statistical computation did not show any significant difference (Table 1). Nitrofurantoin-4 showed better function in acidic pH. Ampicillin and Amoxicillin are resistant to and absorbed much better in acidic pH. On the contrary, Co-trimoxazole is more effective in alkaline pH. In neutral or acidic media it changes to crystal form and precipitate[11]. In spite of the fact that there are no significant statistical differences between two plates (test plate and control plate), It was found the antagonistic effect between Cranberry and two antibiotic disks (*i.e.* Ciprofloxacin-1 and Amikacin-2) (P=0.00). The results show that use of Cranberry with some antibiotics that explained here can diminish the medicinal effects of the antibiotics in Urinary tract infections (UTI) treatments. The awareness about interference and the suppression of the appropriate medicinal effect of antibiotics by *Vaccinium arctostaphylos* can be useful for treating UTIs.

CONCLUSION

The chemical compositions of the different types of Cranerry were investigated. It was determined that this type of medicinal herb was utilized for UTI treatment. *Vaccinium arctostaphylos* genus was used to investigate the synergistic effect of aqueous Cranberry (*Vaccinium arctostaphylos*) extract in association with antibiotics (Ciprofloxacin-1, Amikacin-2, Ampicillin-3 and Nitrofurantoin-4) on isolates of *E. coli* cause UTI, *in vitro*. The results show that use of Cranberry with some antibiotics that have been explained here, can show some interferring effects with the antibiotics and diminish the medicinal effects of the antibiotics (antagonistic effect) in urinary tract infections (UTI) treatment.

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