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Current clinical status on the preventive effects of cranberry consumption against urinary tract infections

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A B S T R A C T

Urinary tract infections (UTIs) represent a common and quite costly medical problem, primarily affecting the female population which may be due to a shorter urethra. The bacterium *Escherichia coli* are mainly responsible for most uncomplicated UTIs. Cranberry antibacterial effects have widely been studied in vitro, and laboratory and clinical studies have also been performed to elucidate the mechanisms of cranberry actions and the clinical benefits of cranberry consumption against UTIs. The present review aimed to summarize the proposed mechanisms of cranberry actions against UTIs and the clinical trials that evaluated the efficacy of supplementing cranberry products in different subpopulations. Taking into consideration the existing data, cranberry consumption may prevent bacterial adherence to uroepithelial cells which reduces the development of UTI. Cranberry consumption could also decreasing UTI related symptoms by suppressing inflammatory cascades as an immunologic response to bacteria invasion. The existing clinical trials suggest that the beneficial effects of cranberry against UTIs seem to be prophylactic by preventing the development of infections; however, they exert low effectiveness in populations at increased risk for contracting UTIs. Additional well-designed, double-blind, placebo-controlled clinical trials that use standardized cranberry products are strongly justified in order to determine the efficiency of cranberry on the prevention of UTIs in susceptible populations.

1. Introduction

Simply stated, a urinary tract infection (UTI) refers to the presence of a certain threshold number of bacteria in the urine, usually 10^5 colony forming U/mL. This condition consists of either cystitis (bacteria in the bladder), urethral syndrome, or pyelonephritis (infection of the kidneys). Although UTIs can occur in both men and women, they are about 50 times more common in adult women compared to adult men, likely due to the presence of a shorter urethra in women [1]. Even more troublesome, UTIs are often recurring: 26.6% of women with a UTI were confirmed to have a second infection within 6 months. The first step for most UTIs is the colonization of periurethral tissues with uropathogenic organisms and then followed by the passage of the bacteria through the urethra. The bacteria proliferate in the otherwise

Abbreviations: UTI, urinary tract infection; *E coli*, Escherichia coli; PACs, proanthocyanidin polymers; UA, ursolic acid; HCA, hydroxycinnamic; HBA, hydroxybenzoic acid; NO, nitric oxide; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-α; LPS, lipopolysaccharide; TMP, trimethoprim; SMX, sulfamethoxazole.

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sterile urinary tract and then adhere to the bladder wall [2]. The bacterium, *Escherichia coli*, is responsible for most of the uncomplicated UTIs. Alarmingly enough, low-dose antibiotic prophylaxis that is currently recommended for preventing UTIs is related to the development of resistance to the causative microorganisms and the indigenous flora. In this aspect, the increasing prevalence of uropathogens, especially *E coli*, that are resistant to antimicrobial agents has stimulated interest in novel non-antibiotic methods for the prevention of UTIs [3].

Cranberries, also referred to as *Vaccinium macrocarpon*, consist of nearly 90% water and are great sources of dietary flavonoids, including anthocyanins and proanthocyanins (PACs) [4]. Augmenting evidence has suggested that cranberries may exert a preventive and therapeutic role in human UTIs. Based on promising in vitro data, several investigators started laboratory and clinical studies to determine the exact mechanism of action, as well as the clinical benefits of cranberry consumption in the management of UTIs. Herein, we aimed to review the basic mechanisms of action of cranberries against UTIs and to summarize current clinical trials that have evaluated their efficacy in the treatment of UTIs in different subpopulations. For this purpose, the Cochrane Library, PubMed, Embase, and Scopus databases were searched for relevant studies using keywords relating to cranberry and UTIs until May 2013 without restrictions and by reviewing the reference lists from retrieved articles.

2. Cranberry phytochemical composition

The chemical composition of the cranberry fruit family, which includes the American species, *V macrocarpon* and the European species, *V oxycoccus* (or *Northern cranberry* and *V microcarpum* or *small cranberry*), has recently been analyzed and several components have been isolated and identified in various fractions. Among them, the flavonoids anthocyanins, flavonols and PACs, catechins or flavan-3-ols, phenolic acid derivatives, and triterpenoid analogues have been identified as the major constituents of the cranberry species (Fig. 1).

The major anthocyanins in cranberries are galactosides and arabinosides of cyanidin and peonidin, and to a lesser extent, malvidin, pelargonidin, delphinidin, and petunidin [5,6]. Apart from monomeric anthocyanins, polymeric anthocyanin-containing color compounds seem to exist in cranberry non-dialyzable material [7]. Moreover, flavonols are found in abundance in cranberry fruits, mostly in glycosylated forms of quercetin, myricetin, isorhamnetin, and kaempferol. Prurin, a flavanone derivative, has been identified, isolated, and characterized in the cranberry fruit [7]. Flavan-3-ols, which are monomers of PACs, and several catechin derivatives have also been reported to exist in cranberries [8,9]. Notably, PACs have been quantified according to the degree of polymerization and not individually. In cranberry fruit they are primarily dimers, trimers, and larger oligomers of epicatechin. They also tend to occur as tetramers to decamers reaching to 23 degrees of polymerization composed of epicatechin units with epigallocatechin and catechin extending units [10]. PACs characterization in cranberry juice cocktail has shown the presence of a series of polyflavan-3-ol oligomers, composed of 4–10 repeating unit structures of epicatechin and epigallocatechin [11].

Cranberry fruit also contains triterpenoid derivatives of the ursane type. The major terpene in cranberries is the pentacyclic triterpene, ursolic acid (UA). UA content of whole cranberry fruit of different cultivars ranges between doses of 60-110 mg/100 g [12]. Two hydroxycinnamic derivatives in whole cranberry fruit in quantities that can average about 15 mg/100 g fresh fruit have mainly been reported [13]. Several sterols, iridoid glycosides, and other terpene derivatives have been isolated from whole cranberry fruit [14]. In addition, the cell wall composition of the cranberries seems to include a number of complex carbohydrates like pectin, cellulose, and hemicellulose [15]. Cranberries contain various sugars like sucrose, glucose, fructose, and sorbitol. Interestingly, apart from the presence of vitamin C in cranberries, a wide variety of vitamins and provitamins have been identified [7,16].

Another family of compounds includes derivatives of hydroxycinnamic and hydroxybenzoic acid in quantities that average about 15-20 mg/100 g fresh fruit and, to a lesser extent, derivatives of salicylic, ellagic, and benzoic acid [12]. The presence of high levels of ellagitannins has been reported, while unusually high levels of benzoates and simple phenolics were verified in cranberry juice, mostly in bound forms in the cell wall polysaccharides or esterified to sugars [17]. Resveratrol, a phenolic, stilbenoid compound with a similar chemical structure compared to the synthetic estrogen agonist diethylstilbestrol, has been isolated at a concentration of 900 ng/g dry weight in cranberry fruits from Nova Scotia (*V macrocarpon*) [18].

3. Cranberry mechanisms of action against UTIs: in vitro evidence

Preliminary studies, aiming to investigate the potential effects of cranberries in UTI prevention and management, have focused on the acidification of urine that was supposed to be caused by cranberry consumption. In the early 1900s, Blatherwick et al reported a reduction in urine pH level (6.4-4.5) with a concomitant increase in excretion of hippuric acid (0.77-4.74 g) after consumption of cooked cranberries. Similarly, several other investigators documented that certain amounts of cranberry juice (450-720 mL daily) lowered urinary pH [19,20]. However, none of the urine samples was bacteriostatic against *E coli*. However, Bodel et al documented that hippuric acid was bacteriostatic at a minimum concentration of 0.02 mmol/L at pH 5.0, while the antibiotic activity of hippuric acid decreased 5-fold as the pH increased to 5.6 [21]. Consequently, it was speculated that cranberry juice could not exert a bacteriostatic effect, since it was not rich enough in hippuric acid and, therefore, did not lower urine pH sufficiently [21]. Afterward, additional investigators confirmed these notions, it is now currently accepted that low concentrations of benzoic acid present in the fruit (0.1% of weight), along with the limited amount of cranberry that can be consumed daily, may rarely result in adequate hippuric acid excretion to achieve bacteriostatic urinary concentrations [22]. In other