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Review

Monograph of *Vaccinium macrocarpon*

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Cranberry (*Vaccinium macrocarpon*) is a very useful drug in Unani system of medicine and Ayruvedic system of medicine. Research has suggested cranberry may be effective against UTIs (urinary tract infection) because it prevents *Escherischia coli*, the bacteria that cause most urinary tract infections, from attaching to the walls of the bladder. It only grows in open, sunny, wet areas in the colder regions of the Northern Hemisphere. Cranberry is a small evergreen shrub grown in bogs in damp forests and open ponds. So many studies have been done on pharmacological activities of cranberry fruits.

Key words: *Vaccinium macrocarpon*, *Escherischia coli*, urinary tract infections.

INTRODUCTION

Botanical name: *Vaccinium macrocarpon*
Family name: Ericaceae
Common name: American cranberry, large cranberry.
Part used: Berries.

History

The cranberry (Figure 1), along with the blueberry and concord grape, is one of North America's three native fruits that are commercially grown. Cranberries were first used by Native Americans, who discovered the wild berry's versatility as a food, fabric dye and healing agent. Today, cranberries are commercially grown throughout the northern part of the United States and are available in both fresh and processed forms. Its effectiveness in treating urinary tract infection is scientifically proven. Urinary tract infections are caused by bacteria. The most common causative bacteria are *Escherischia coli, Streptococcus, Enterobacter, Klebsiella and Proteus* species. They grow and multiply in number in the bladder to cause bladder or urinary tract infections.

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Habitat

Cranberry only grows in open, sunny, wet areas in the colder regions of the Northern Hemisphere.

Plant description

It is a native shrub of 4 m high, with upright, spreading, arching branches. Leaves deciduous, opposite, ovate, 5 to 12 cm long, deeply 3-lobed, coarsely toothed, with 1 to 6 large glands near the petiole apex, becoming yellow-red or reddish-purple in the fall. Flowers white, in flat-topped clusters 7 to 10 cm broad, with flowers of two different types, those in the outer ring sterile, showy, with expanded corollas 1 to 2 cm broad, the inner flowers much smaller, fertile, with yellow anthers. Fruit berry-like (a drupe), globose, bright red, 8 to 10 mm in diameter; stone single, strongly flattened. The pink flowers are followed by small reddish-black berries in June or July (Figure 2).

Traditional medicinal use of cranberry fruit

i) Traditional medicinal use of cranberry fruit by Native Americans was primarily for the treatment of bladder and kidney ailments (Boon et al., 2004).

Figure 1. Cranberry fruits.

Figure 2. Cranberry plant.

ii) There has also been a relatively long history of scientific research on this herbal remedy, dating back to its chemical characterization in the late 19th century (Raz et al., 2004). Cranberry's principal therapeutic value today continues to be for the treatment and prevention of urinary tract infections (Lynch et al., 2004).

iii) It was originally thought that cranberry's biological activity was due to an acidifying effect on urine; however, this theory has been largely disproved. The currently accepted mechanism of action in treating and preventing urinary tract infections is through disabling *E. coli* capacity to adhere to the urethra (Raz et al., 2004; Liu et al., 2006).

iv) The fruit contains two compounds, fructose and a

proanthocyanidin, that adhere to proteins on the fimbriae of *E. coli,* effectively inhibiting the bacteria from sticking to the epithelial cell lining of the urethra (Raz et al., 2004; Liu et al., 2006).
v) Without the ability to establish a strong foothold through adherence, the infection is either attenuated or prevented at the outset. The pregnant woman, along with a number of other issues, has to deal with an increased frequency of urinary tract infections (D'Souza et al., 2004; Sheikh et al., 2000).
vi) Given the recognised safety of cranberry juice and its efficacy in the treatment of urinary tract infections (Raz et al., 2004; Drug, 2005).
vii) It is of no surprise that this therapy is widely used by pregnant women. A survey of 400 women from Norway found that cranberry fruit juice was the most commonly used herbal therapy during pregnancy (Nordeng et al., 2004).
viii) The popular use of this herb during pregnancy calls for an in-depth understanding of its efficacy and potential for harm during pregnancy and lactation.

Uses of cranberry in urinary tract infection

Urinary tract infection – background urinary tract infections (UTIs) are common, painful and disruptive (Ellis et al., 2000). 11% of the female population in the United States reports having had at least one UTI a year (Foxman et al., 2000). And an additional 2 to 5% of all women have UTI recurrences once or twice a year (Walker et al., 1997). The pathogen responsible for over 85% of all UTIs is *E. coli* (Leahy et al., 2004; Sobel et al., 1991). Diagnosed UTIs are typically treated with a course of antibiotics. The incidence and virulence of UTIs has prompted a great deal of research into the role of cranberry juice plays in the prevention of this uncomfortable condition. Urine is normally sterile, so in order for disease to occur, pathogenic microorganisms must first enter the urethra and adhere to host tissue. Once attached, bacteria are able to proliferate and subsequently cause clinical symptoms of infection (Kuzminski et al., 1996).

Protection against antibiotic resistant *E. coli*

Given mounting concern over the increase in antibiotic resistant *E. coli* bacteria (Manges et al., 2001) researchers are focusing more attention on alternative measures for the prevention and alleviation of UTI symptoms (Reid et al., 2002). In fact, a recent study found that urine collected from women who drank 250 ml (8.5 fluid ounces) of cranberry juice cocktail prevented the adhesion of 80% of 39 P-fimbriated *E. coli* isolates tested and 79% of the 24 antibiotic resistant strains (Howell et al., 2002). The antiadhesion activity in the subject's urine was noticeable 2 h after cranberry juice consumption and lasted up to 10 h. Of particular interest, these researchers noted that the mechanism by which cranberry juice prevents bacterial adhesion is not likely to increase selective pressure for antibiotic resistant strains.

Proposed mechanism of action

To date the collective data suggest two possible mechanisms of action in the preventive antiadhesion activity of cranberries: A-type PACs are metabolized relatively intact and collect in the urine to provide protective effects from bacteria that migrate from the perineum and vagina; and/or the PACs eliminated through the colon bind to uropathogenic bacteria thus decreasing the virulence of these microbes if they come in contact with the uroepithelium. Indeed, researchers have found that cranberry PACs are absorbed into the bloodstream, accounting for the former preventive effect (Howell et al., 2001).

Chemical constituents

The predominant flavonoids present in cranberries include the anthocyanins, flavonols and flavan-3-ols (particularly proanthocyanidins). In cranberries, the 6 major anthocyanins are peonidin-3-galactoside, cyanidin-3-galactoside, cyanidin-3-arabinoside, peonidin-3-arabinoside, peonidin-3-glucoside and cyanidin-3-glucoside (Table 1). Quantities of these anthocyanins were reported in cranberry juice cocktail to be 2.8, 2.0, 1.4, 1.1, 0.3 and 0.2 ppm, respectively (Cunningham et al., 2004; Hong et al., 1990; Prior et al., 2007).

PHARMACOLOGICAL ACTIVITY OF PHENOLIC ACIDS IN CRANBERRY

Enhancing health benefits of berries through phenolic antioxidant enrichment

Emerging epidemiological evidence is increasingly pointing to the beneficial effects of fruits and vegetables in managing chronic and infectious diseases. These beneficial effects are now suggested to be due to the constituent phenolic phytochemicals having antioxidant activity. Cranberry like other fruits is also rich in phenolic phytochemicals such as phenolic acids, flavonoids and ellagic acid (Figure 4). Consumption of cranberry has been historically been linked to lower incidences of urinary tract infections and has now been shown to have a capacity to inhibit peptic ulcer-associated bacterium, *Helicobacter pylori*. Isolated compounds from cranberry have also been shown to reduce the risk of cardiovascular diseases. Recent evidence suggests the

Table 1. Major classes of phenolic phytochemicals identified in cranberries.

Class	Subclass	Compound
Phenolic acid	Benzoic acid	
	Hydroxycinnamic	p-Coumaric acid Sinapic Caffeic Ferulic
	Ellagic acid	
Flavonoids	Flavonols	Quercetin Myricetin
	Flavan-3-ols	Proanthocyanidins Epicatechin Anthocyanins Cyanidin Peonidin
Stilbenes		Resveratrol

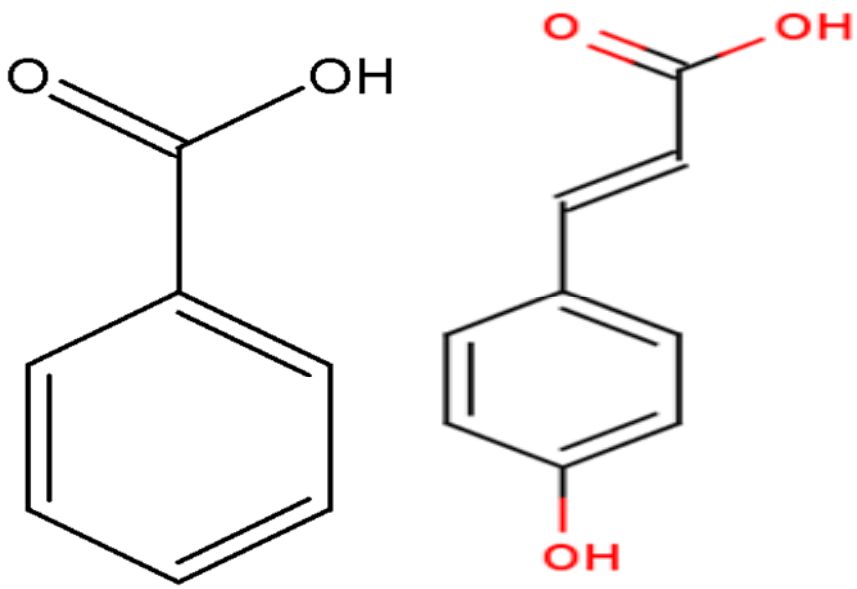

Figure 3. Benzoic acid.

ability of phytochemical components in whole foods in being more effective in protectively supporting human health than compared to isolated individual phenolic phytochemicals. This implies that the profile of phenolic phytochemicals determines the functionality of the whole food as a result of synergistic interaction of constituent phenolic phytochemicals (Figures 3 and 4) (Vattem et al., 2005).

Pharmacological activities of quercetin in cranberry

Anti inflammatory and anti cancer activity of quercitin

Cranberry (*V. marcocarpon*) fruit and quercetin, a major flavonoid found in cranberries, are likely contributors to chemoprevention, and their anti-inflammatory activities

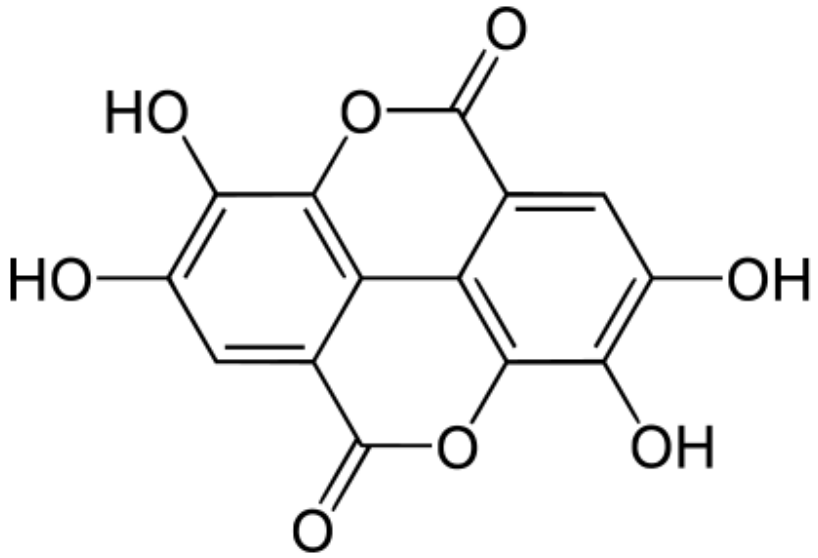

Figure 4. Ellagic acid.

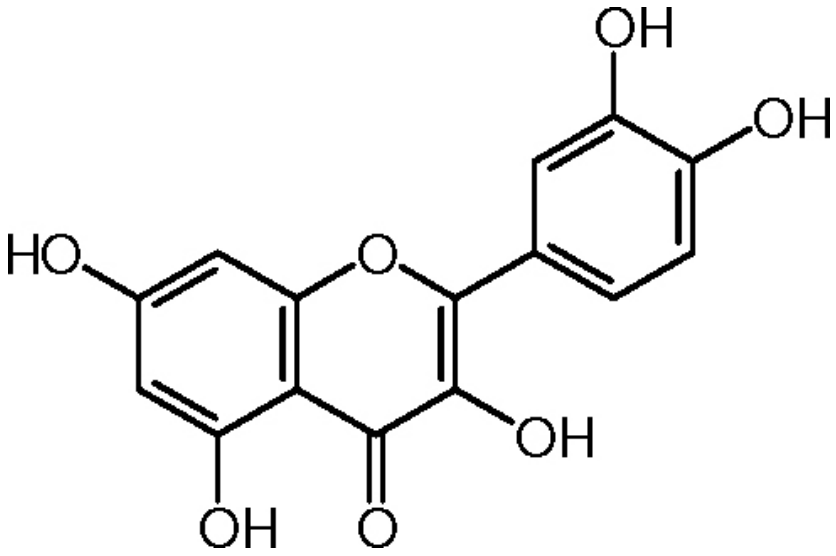

Figure 5. Quercetin.

may play a potential role in colon cancer prevention (Figure 5) (Narayansingh et al., 2009).

Pharmacological activities of Proanthocyanidins

The proanthocyanidins inhibit dimethylnitrosamine-induced liver damage in rats

Proanthocyanidins are naturally occurring compounds widely available in fruits, vegetables, nuts and seeds. Proanthocyanidins exhibited *in vivo* hepatoprotective and anti-fibrogenic effects against DMN-induced liver injury. It suggests that grape seed proanthocyanidins may be useful in preventing the development of hepatic fibrosis (Shin et al., 2010).

Anticancer effects of oligomeric proanthocyanidins

Ol igomeric proanthocyanidins (OPC), natural polyphenolic compounds found in plants, are known to have antioxidant and anti-cancer effects (Kim et al., 2005).

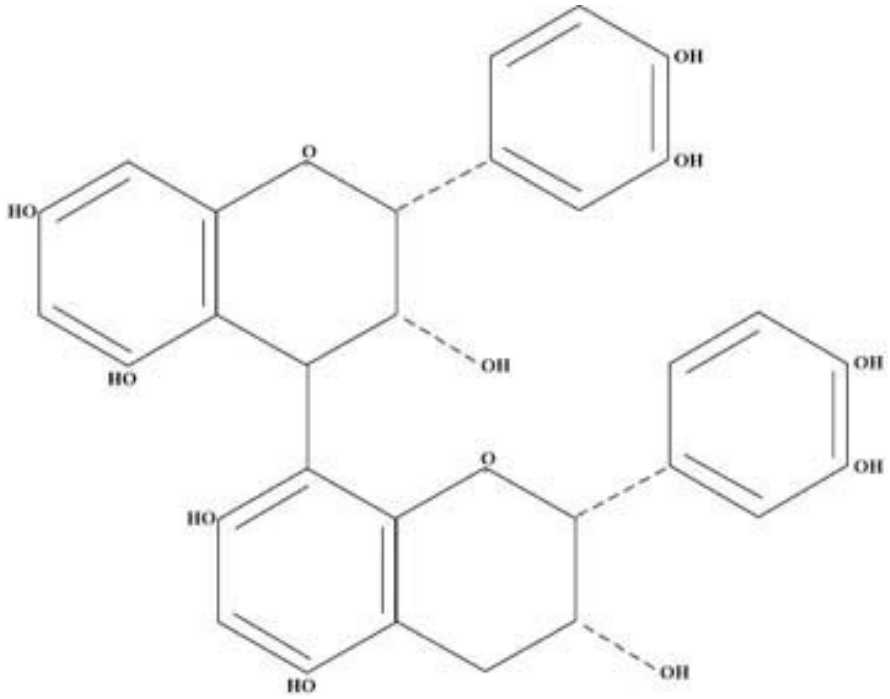

Figure 6. Proanthocyanidin.

Inhibit MMP production and activity

Matrix metalloproteinases (MMPs) produced by resident and inflammatory cells in response to periodontopathogens play a major role in periodontal tissue destruction.AC-PACs inhibited the production of MMPs in a concentration-dependent manner. Furthermore, the catalytic activity of MMP-1 and MMP-9 was also inhibited (La et al., 2009).

IMPORTANCE IN HUMAN HEALTH AND DISEASE PREVENTION

Oligomeric proanthocyanidins, naturally occurring antioxidants widely available in fruits, vegetables, nuts, seeds, flowers and bark, have been reported to possess a broad spectrum of biological, pharmacological and therapeutic activities against free radicals and oxidative stress. GSPE is highly bioavailable and provides significantly greater protection against free radicals and free radical-induced lipid peroxidation and DNA damage than vitamins C, E and b-carotene. GSPE was also shown to demonstrate cytotoxicity towards human breast, lung and gastric adenocarcinoma cells, while enhancing the growth and viability of normal human gastric mucosal cells (Bagchi et al., 2000).

Inhibit tumor cell growth

Whole cranberry extract and the proanthocyanidin fractions were screened for effect on the expression of matrix metalloproteinases in DU 145 prostate carcinoma cells. The expression of MMP-2 and MMP-9 was inhibited in response to whole cranberry extract and to a lesser degree by the proanthocyanidin fractions (Figure 6) (Catherine et al., 2005).

CONCLUSION

Cranberry (*V. macrocarpon*) is very useful drug in Unani system of medicine and ayruvedic system of medicine. After reviewing of cranberry research data suggested cranberry may be effective against UTIs because it prevents *E. coli*, the bacteria. Moreover there is nee to cultivate this useful medicinal plant to overcome urinary tract infections.

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