

Cranberry

Species (Family)

Vaccinium macrocarpon Ait, *Vaccinium oxycoccus* (Ericaceae)

Synonym(s)

Large Cranberry (*V. macrocarpon*) is the species grown for commercial purposes.⁽¹⁾ *V. oxycoccus* is European Cranberry, Mossberry and Small Cranberry.

Part(s) Used

Fruit (whole berries)

Pharmacopoeial and Other Monographs

Martindale 32nd edition^(G43)

Legal Category (Licensed Products)

Cranberry is not included in the GSL.^(G37)

Constituents

Acids Citric, malic, quinic and benzoic acids are present.⁽²⁾

Carbohydrates Fructose and oligosaccharides.

Phenolics Anthocyanins and proanthocyanidins.

Other constituents Trace glycoside has been isolated from *V. oxycoccus*.⁽³⁾ Cranberries are also a good source of fibre. Cranberry juice cocktail contains more carbohydrate than do products (i.e. soft or hard gelatin capsules) based on cranberry powder (prepared from rapidly dried fruits), whereas the latter contain more fibre.⁽²⁾ Alkaloids (*N*-methylazatriicyclo type) have been isolated from the leaves.⁽⁴⁾

Food Use^(G32)

Cranberries are commonly used in foods;⁽⁵⁾ cranberry juice cocktail (containing approximately 25% cranberry juice) is widely available.^(2,5) Cranberry is listed by the Council of Europe as a natural source of food flavouring (fruit: category 1) (see Appendix 23).^(G17)

Herbal Use^(G32)

Cranberry juice and crushed cranberries have a long history of use in the treatment and prevention of urinary tract infections.⁽¹⁾ Traditionally, cranberries have also been used for blood disorders, stomach ailments, liver problems, vomiting, loss of appetite, scurvy and in the preparation of wound dressings.⁽⁵⁾

Dosage

The doses used in clinical trials of cranberry for prevention of urinary tract infections have been variable. One study used 300 mL cranberry juice cocktail (containing 30% cranberry concentrate) daily for six months.⁽⁶⁾

Pharmacological Actions

Documented activity for cranberry is mainly of its use in the prevention and treatment of urinary tract infections; its role in urinary tract infection has been reviewed.⁽¹⁾

Initially it was thought that the antibacterial effect of cranberry juice was due to its ability to acidify urine and, therefore, to inhibit bacterial growth. However, recent work has focused on the effects of cranberry in inhibiting bacterial adherence and on determining anti-adhesion agents in cranberry juice. Bacterial adherence to mucosal surfaces is considered to be an important step in the development of urinary tract infections;⁽⁷⁾ it is facilitated by fimbriae (proteinaceous fibres on the bacterial cell wall) which produce adhesins that attach to specific receptors on uroepithelial cells.⁽⁸⁾

In vitro and animal studies

In *in vitro* studies using human urinary tract isolates of *Escherichia coli*, cranberry cocktail (which contains fructose and vitamin C in addition to cranberry juice) inhibited bacterial adherence to uroepithelial cells by 75% or more in over 60% of the clinical isolates.⁽⁹⁾ In addition, urine from mice fed cranberry juice significantly inhibited *E. coli* adherence to uroepithelial cells when compared with urine from control mice.⁽⁹⁾ However, these studies did not define the bacteria tested in terms of the type of fimbriae they might have expressed (specific fimbriae mediate bacterial adherence to cells).

Irreversible inhibition of adherence of urinary isolates of *E. coli* expressing type 1 and type P fimbriae has been demonstrated with cranberry juice cocktail.⁽¹⁰⁾ It was thought that fructose might be responsible for the inhibition of type 1 fimbriae⁽¹⁰⁾ and an unidentified high molecular weight substance responsible for type P fimbriae inhibition.⁽¹¹⁾ Further *in vitro* studies in which cranberry juice was added to the growth medium of P-fimbriated *E. coli* duplicated immediate inhibition of adherence, but also showed the loss of fimbriae with cellular elongation after long-term exposure; such changed bacteria are unable to adhere to urothelium.⁽¹²⁾

Proanthocyanidins extracted from cranberries have been shown to inhibit the adherence of P-fimbriated *E. coli* to uroepithelial cell surfaces at concentrations of 10–50 µg/mL, suggesting that proanthocyanidins may be important for the stated effects of cranberry in urinary tract infections.⁽¹³⁾

The effects of a high molecular weight constituent of cranberry juice on adhesion of bacterial strains found in the human gingival crevice have also been investigated.⁽¹⁴⁾ A non-dialysable material derived from cranberry juice concentrate used at concentrations of 0.6–2.5 mg/mL reversed the interspecies adhesion of 58% of 84 bacterial pairs. Gram-negative dental plaque bacteria appeared to be more sensitive to the inhibitory effects of the cranberry constituent on adhesion.⁽¹⁴⁾

Crude extracts of cranberry have been reported to exhibit potential anticarcinogenic activity *in vitro* as demonstrated by inhibition of the induction of ornithine decarboxylase (ODC) by the tumour promoter phorbol 12-myristate 13-acetate (TPA).⁽¹⁵⁾ The greatest activity appeared to be in the polymeric proanthocyanidin fraction which had an IC₅₀ for ODC activity of 6.0 µg. The anthocyanidin fraction and the ethyl acetate extract were either inactive or relatively weak inhibitors of ODC activity.

A cranberry extract with a polyphenolic content of 1548 mg gallic acid equivalents per litre inhibited low-density lipoprotein (LDL) oxidation *in vitro*.⁽¹⁶⁾

Cranberry juice has demonstrated marked *in vitro* antifungal activity against *Epidermophyton floccosum* and against several *Microsporium* and *Trichophyton* species, but had no effect against *Candida albicans*.⁽¹⁷⁾ Benzoic acid and/or other low molecular weight constituents of cranberry juice were reported to be responsible for the fungistatic action.

Clinical studies

Clinical trials investigating the use of cranberries for the treatment⁽¹⁸⁾ and prevention⁽¹⁹⁾ of urinary tract infections have been subject to Cochrane systematic reviews; both of these systematic reviews sought to

include all randomised or quasi-randomised controlled trials.^(18,19)

Prevention of urinary tract infections Four trials^(6,20–22) were included in a systematic review of cranberries for prevention of urinary tract infections; three trials compared the effectiveness of cranberry juice versus placebo or water and one trial compared cranberry capsules with placebo.⁽¹⁹⁾ Three of the four trials reported beneficial effects for cranberry compared with placebo on at least one of the outcomes (number of symptomatic or asymptomatic urinary tract infections, side-effects, adherence to therapy). However, the methodological quality of the trials was found to be poor and the reliability of the results questionable. It was stated that ‘on the basis of the available evidence, cranberry juice cannot be recommended for the prevention of urinary tract infections in susceptible populations’.⁽¹⁹⁾

The largest study of cranberry juice for the prevention of urinary tract infections was a double-blind, placebo-controlled trial involving 153 women (mean age 78.5 years) randomised to receive 300 mL cranberry juice cocktail ($n = 72$) or an indistinguishable placebo ($n = 81$) daily for six months.⁽⁶⁾ The odds of experiencing bacteriuria with pyuria were significantly lower in cranberry-treated subjects than in those who received a placebo beverage ($p = 0.004$). A randomised, controlled, crossover study was conducted involving 38 persons (mean age 81 years) who had had hospital treatment and were waiting to be transferred to a nursing home.⁽²¹⁾ Subjects received cranberry juice (15 mL) mixed with water or water alone twice daily for four weeks before crossing over to the alternative regimen. Seventeen participants completed the study and, of the seven from whom data were suitable for comparison, there were fewer occurrences of bacteriuria during the period of treatment with cranberry juice.⁽²¹⁾

The role of cranberry in the prevention of urinary tract infections in younger women has been explored in a randomised, double-blind, placebo-controlled, crossover trial involving 19 non-pregnant, sexually active women aged 18–45 years.⁽²²⁾ Participants received capsules containing 400 mg cranberry solids daily (exact dose not stated) or placebo for three months before crossing over to the alternative regimen. Ten subjects completed the six-month study period. Of the 21 incidents of urinary tract infection recorded among these participants, significantly fewer occurred during periods of treatment with cranberry than with placebo ($p < 0.005$).⁽²²⁾

A randomised, physician-blind, crossover study investigated the efficacy of cranberry cocktail (30% cranberry concentrate) (15 mL/kg/day) for six

months in 40 children (age range 1.4–18 years, mean age 9.35 years) with neuropathic bladder and managed by clean intermittent catheterisation; water was used as a control.⁽²⁰⁾ No benefit was reported for cranberry compared with control.

A randomised, double-blind, placebo-controlled, crossover trial of the effects of consumption of cranberry concentrate on the prevention of bacteriuria and symptomatic urinary tract infection has been carried out in children ($n = 15$) with neurogenic bladder receiving clean intermittent catheterisation.⁽²³⁾ Children drank 2 oz of cranberry concentrate or placebo daily for three months before changing to the alternative regimen. At the end of the study, the number of urinary tract infections occurring under each regimen was identical ($n = 3$). There was no significant difference between cranberry treatment and placebo with regard to the number of collected urine samples testing positively for a pathogen (75% of samples for both cranberry and placebo) ($p = 0.97$). It was concluded that cranberry concentrate had no effect on the prevention of bacteriuria in the population studied.⁽²³⁾

Treatment of urinary tract infections Although several trials investigating the effectiveness of cranberry juice and cranberry products for treating urinary tract infections were found, none of these trials met all the inclusion criteria for systematic review.⁽¹⁸⁾ Two of the studies found^(24,25) did report a beneficial effect with cranberry products, although both contained methodological flaws and no firm conclusions can be drawn from these studies.⁽¹⁸⁾ Thus, it was stated that 'at the present time, there is no evidence to suggest that cranberry juice or other cranberry products are effective in treating urinary tract infections' (see Pharmaceutical Comment).⁽¹⁸⁾

Other studies Early studies involving the administration of large amounts of cranberry juice to human subjects reported reductions in mean urinary pH values.^(26,27) A crossover study involving eight subjects with multiple sclerosis reported that administration of cranberry juice and ascorbic acid was more effective than orange juice and ascorbic acid in acidifying the urine. However, neither treatment consistently maintained a urinary pH lower than 5.5, the pH previously determined as necessary for maintaining bacteriostatic urine.⁽²⁸⁾ Inhibition of bacterial adherence (see *In vitro* and animal studies) has been observed with urine from 22 human subjects who had ingested cranberry cocktail 1–3 hours previously.⁽⁹⁾ Protection against bacterial adhesion has also been reported in a study involving urine collected from ten healthy male volunteers who had ingested

water, ascorbic acid (500 mg twice daily for 2.5 days) or cranberry (400 mg three times daily for 2.5 days) supplements.⁽²⁹⁾ Urine samples were used to determine uropathogen adhesion to silicone rubber in a parallel plate flow chamber; urine obtained after ascorbic acid or cranberry supplementation reduced the initial deposition rates and numbers of adherent *E. coli* and *Enterococcus faecalis*, but not *Pseudomonas aeruginosa*, *Staphylococcus epidermidis* or *C. albicans*.

Other preliminary studies have explored the use of cranberry juice in reducing urine odours,⁽³⁰⁾ in improving peristomal skin conditions in urostomy patients⁽³¹⁾ and in reducing mucus production in patients who have undergone entero-uroplasty.⁽³²⁾

The ingestion of cranberry juice by subjects with hypochlorhydria due to omeprazole treatment or atrophic gastritis has been shown to result in increased protein-bound vitamin B₁₂ absorption, although the clinical benefit of ingesting cranberry juice along with a meal (i.e. with the buffering action of food) remains to be determined.⁽³³⁾ Possible mechanisms by which the ingestion of an acidic drink such as cranberry juice could result in improved protein-bound vitamin B₁₂ absorption include increased release of vitamin B₁₂ from protein by direct action of acid on the vitamin B₁₂–protein bond and a pH-sensitive bacterial binding activity of vitamin B₁₂ that is altered in an acidic environment.⁽³³⁾

Side-effects, Toxicity

None documented for cranberry, although diarrhoea is possible if large quantities are consumed.^(G31) One study has reported that no subjects withdrew because of undesirable side-effects,⁽²²⁾ although this study involved only a small number ($n = 19$) of patients. A systematic review of cranberry products for the prevention of urinary tract infections reported that the drop-out rates in the four studies included^(6,20–22) were high (20–55%).⁽¹⁹⁾ In one of these studies, of 17 withdrawals during cranberry treatment (a further two occurred during the control period), nine participants gave the taste of cranberry as the reason for withdrawal.⁽²⁰⁾

It has been claimed that ingesting large amounts of cranberry juice may result in the formation of uric acid or oxalate stones secondary to a constantly acidic urine and because of the high oxalate content of cranberry juice.⁽¹⁾ However, it has also been stated that the role of cranberry juice as a urinary acidifier has not been well established.⁽³⁴⁾ The use of cranberry juice in preventing the formation of stones which develop in alkaline urine, such as those

comprising magnesium ammonium phosphate and calcium carbonate, has been described.⁽²⁶⁾

Contra-indications, Warnings

The calorific content of cranberry juice should be borne in mind. Patients with diabetes who wish to use cranberry juice should be advised to use sugar-free preparations. Patients using cranberry juice should be advised to drink sufficient fluids in order to ensure adequate urine flow.^(G31) Although a constituent of cranberry juice has been reported to have potential for altering the subgingival microbiota, some commercially available cranberry juice cocktails may not be suitable for oral hygiene purposes because of their high dextrose and fructose content.⁽¹⁴⁾

It has been stated that cranberry should be used with caution in patients with benign prostatic hyper trophy or urinary obstruction, because there is the theoretical possibility that cranberry may enhance the elimination of drugs excreted in urine.^(G31) Interference with dipstick tests for glucose and haemoglobin in urine has been reported in a study involving 28 patients who had drunk 100 or 150 mL of low-sugar or regular cranberry juice daily for seven weeks;⁽³⁵⁾ ascorbic acid in cranberry juice was reported to be the component responsible for interference resulting in negative test results.

Pregnancy and lactation. There are no known problems with the use of cranberry during pregnancy. Doses of cranberry greatly exceeding the amounts used in foods should not be taken during pregnancy and lactation.

Pharmaceutical Comment

Limited chemical information is available for cranberry. Documented *in vitro* and animal studies provide supporting evidence for a mechanism of action for cranberry in preventing urinary tract infections. However, little is known about the specific active constituent(s); proanthocyanidins have been reported to be important.⁽¹³⁾

Preliminary clinical trials of cranberry for the prevention of urinary tract infections have generally been uncontrolled and/or involved only small numbers of patients. The validity of the results of a controlled trial involving relatively large numbers of (female only) patients⁽⁶⁾ was questioned because of methodological shortcomings in the study design, particularly the method of randomisation.^(36,37) Other controlled studies claiming to involve random assignment to treatment⁽²⁰⁻²²⁾ either did not employ true randomisation⁽²¹⁾ or the method of randomisation was not stated.^(20,22) In addition, these four

controlled studies^(6,20-22) differed in the formulations of cranberry, doses and treatment periods used. Therefore, clinical studies do not provide compelling evidence for the efficacy of cranberry in the prevention of urinary tract infections, nor do they provide evidence that it is not efficacious. However, the findings do indicate that the area warrants further investigation. Cochrane systematic reviews of cranberry for the treatment and prevention of urinary tract infections have stated that, at present, there is no reliable evidence to suggest that cranberry juice or other cranberry products are effective.^(18,19) It has also been stated that properly randomised, double-blind, placebo-controlled, parallel group trials using appropriate outcome measures are needed in order to determine the efficacy of cranberry products in the prevention and treatment of urinary tract infections.^(18,19) Prevention trials should be of at least 6-months' duration in order to take into account the natural course of the illness.⁽¹⁹⁾

Patients wishing to use cranberry for urinary tract infections should be advised to consult a pharmacist, doctor or other suitably trained health care professional for advice.

References

See also General References G31 and G43.

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