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Exploring Cranberry's Potential In Uti Approach To Uropathogenic Resistance.

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Abstract: Urinary tract infections (UTIs) are prevalent, especially among women, and are often recurrent. This review explores the potential role of cranberry juice in UTI prevention, focusing on its primary active compounds—proanthocyanidins (PACs)—and their anti-adhesive properties against Uropathogenic Escherichia coli (UPEC). PACs inhibit bacterial adhesion to the urinary tract line, which may reduce infection rates. While clinical trials have reported mixed results, certain studies suggest a beneficial effect of cranberry products in lowering UTI recurrence in high-risk populations. This review discusses cranberries's active constituents, mechanisms of action and clinical efficacy, as well as limitations in current research, including variability in cranberry product formulations and dosages. Given concerns over antibiotic resistance, cranberries could serve as a non-antibiotic prophylactic option for UTI management.

Keywords: Proanthocyanidins (PACs), Anti-adhesion, Escherichia coli (E. coli), UTI recurrence prevention, Biofilm inhibition, Natural remedies for UTI, Cranberry PACs mechanism of action, Antibiotic resistance.

Introduction: UTIs are widespread bacterial illnesses that afflict millions of people worldwide, particularly women. Cranberry juice has long been used to prevent UTIs. *Escherichia coli* (E. coli), a bacteria that sticks to the lining of the urinary tract, is the main cause of UTIs. According to research, cranberry juice may help prevent UTIs by preventing uropathogenic bacteria—especially E. coli—from adhering to uroepithelial cells. Cranberry juice's proanthocyanidins (PACs) and organic acids, such as quinic acid, malic acid, shikimic acid and citric acids are primarily responsible for its health benefits. Cranberry PACs interrupt the infection process by preventing E. coli with P fimbriae from adhering to urinary tract surfaces. These organic acids also have antibacterial qualities, which lower the number of germs in experimental models of urinary tract infections. [1]

Cranberry juice has been researched as a possible defense against UTIs, especially in women who are more likely to have infections frequently. More than 50% of women will get a UTI at some point in their lives and a sizable portion will cope with recurring episodes. Although antibiotics are frequently used for both prevention and treatment, the possibility of antibiotic resistance has raised interest in alternate approaches, such as dietary supplements.

Proanthocyanidins (PACs), which are found in cranberries are thought to prevent the bacteria E. coli, which is the main cause of UTIs, from sticking to the bladder wall. Infection rates may be lowered by this anti-adhesive characteristic. Research on cranberry products has yielded conflicting results; some have suggested that regular consumption of cranberry extract or juice may reduce the recurrence of UTIs. [2]

Botany:

fig: cranberry plant seeds (stevens cranberry) [58]

A member of the *Ericaceae* family, cranberries are sometimes referred to as *Vaccinium macrocarpon, V. oxycocus, and V. eruthrocarpum*. The cranberry is a contraction of the word "crane berry"; this *bilberry blossom* is the source of its name. The blossom is bell-shaped and white or light rose in color. In June or July, little red berries appear in the northern hemisphere. The fruit has a pulpy texture and the pericarp is parenchymatous, soft, and sour [3, 4].

This little evergreen shrub grows in humid, acid swamps (bogs) that are home to peat moss. It was first found in the northeastern United States, close to the Cape Cod woods. Home gardens seldom ever grow it. Its native Americans have been using it for thousands of years as a way to add flavor to dried meat and as a medication. Sailors have also utilized it because of its high vitamin C content to avoid scurvy content. [3,4]

The US states of Massachusetts, New Jersey and Wisconsin provide 90% of the world's yearly supply (50 million tons = 200 billion fruits), with 8% coming from the British Columbia and Quebec provinces in Canada. In September, the fruit is gathered and in October. Cranberries were in the "top ten" of remedies that US herbalists sell. The typical fresh wholeberries, gelatinized goods and juices (typically 10–25%) are among the preparations of pure juice as well as pills. Pure juice is also unpleasant and acidic (pH of 2.5), even when diluted with conventional sweetening agents. [3,4]

Chemical Constituents: [6,7,8,9]

Table 1:

0rganic acids	Flavonoids	Iridoid glycosides	Anthocyanidins
benzoic acid	(-)-epicatechin	coumaroyl	cyanidin
o-hydroxybenzoic acid	catechin	monotropein	peonidin
m-hydroxybenzoic acid	quercetin	6,7-dihydromonotropein	pelargonidin
p-hydroxybenzoic acid	methoxy quercetin		petunidin
2,3-dihydroxybenzoic acid	dimethoxy myricetin		proanthocyanidin (trimer a-type, dimer a-type,

			dimer b-type)
trans-cinnamic acid	myricetin		
o-hydroxycinnamic acid	methoxy myricetin		
o-phthalic acid	phlorizin		
vanillic acid	prunin		
citric acid			
p-coumaric acid			
ferulic acid			
3-o-p-hydroxycinnamoyl-ursolic acid			
mallic acid			
shikimic acid			
quinic acid			
sinapic acid			
caffeic acid			
trans-resveratrol			

Composition:

In addition to a complex blend of organic acids, vitamin C, flavonoids, anthocyanidins, catechins and triterpenoids, cranberries comprise 88% water. [10,3,4] There are at least 248 distinct constituents in the low-polarity concentrate fraction subfraction.[11]

Cranberries contain at least 14 different organic acids (table I). [6,7] Cranberry juice also contains salicylic acid, although at a concentration of 7 mg/L, about [13]. Cranberry juice's hydrophilic portion contains quinic, malic, citric, and shikimic acids in amounts of 2.67 to 3.57% w/v. [6] At least 22 different kinds of cranberry powder contain flavonoids (table I). Where myricetin and quercetin are the most common (table I). [8, 13] The glycosides of iridoids are in charge of giving cranberry products their flavour. [6] High concentrations of vitamin C can be found in 200 mg/kg of fresh cranberries.[13]

Only vaccinium berries (blueberries, cranberries) contain the tannins (stable polyphenols) known as anthocyanidins and proanthocyanidins. They serve as a natural defence mechanism for plants against microorganisms. The amount of cyanidin varies between blueberries and cranberries with epicatechins being the main component of cranberries. [10,3,4]

The primary forms of cyanidin in cranberry juice are 3-O-arabinoside (16.1%) and 3-O-galactoside (19.7%), and 3-O-arabinoside (35.3%) and 3-O-galactoside (26.8%) of peonidin anthocyanidins. [9] According to the proanthocyanidins, believed to be the primary active ingredients in cranberries, which inhibit uropathogenic type I and P-fimbriated E. coli from adhering to the mucosa of the urogenital tract. These a sequence of oligomers of polyflavan-3-ol having mostly units of epicatechin, mostly in the form of 37% pentamers and 49% tetramers. They are real in stereochemical form in 2,3-cis with at least one

interflavonyl connection of the A-type (C4/C8). The procyanidin A2 is the most often used termination unit. [14,15]

Mechanism of Action:

Therefore, the primary way that cranberries seem to prevent UTIs is by preventing uropathogen P-fimbriae from binding through mannose-specific, lectin-like structures, residues on mucosal cells that resemble mannose. The specific impacts of cranberries on the relationship between fimbriae, bacteria and their mucosal receptors are unknown. On the other hand, research has shown that cranberries weaken the binding between these two moieties and also modify the surface macromolecule's structure. The P-fimbria's equilibrium length is shortened between 148 and 48 nm; proteins are more compacted in this range. [16] P-fimbriae inhibition is perceived to be unchangeable. In bacteria that are 100% inhibited, it is impossible to observe P-fimbriae with electron microscopy and these bacteria grow longer. [17] If P-fimbriae are eliminated in accordance with the impact of cranberries. [10,3,4]

The following describes the mechanism or mechanisms of action of cranberries in preventing urinary tract infections. The theory that cranberry functions by acidifying the urine (improved metabolism and excretion of salicylate conversion of benzoic and quinic acids to hippuric acid in vivo) cannot be sustained. People are unable to consume enough cranberry juice to produce enough hippuric acid in order to generate a bacteriostatic action. Furthermore, urinary acidifiers that are not antibacterial ammonium chloride, for example, does not stop UTIs. [10,3,4] The idea that cranberries operate by preventing adhesion. Uropathogens that I-fimbriated with uroepithelial cells lack support as well and are mediated by their fructose concentration. There is no evidence that fructose alone functions in this way. [10,3,4]

The interaction between bacteria and uroepithelial cells under the effect of cranberry juice (0–27 weight percent) has recently been assessed using a thermodynamic technique. The pair among the organisms examined were E. coli HB101pDC1 (non-fimbriated) and P-fimbriated. During the E. coli HB101pDC1 interaction together with uroepithelial cells, the Gibbs constant negative free energy of adhesion indicated favourable adhesion and these values were unaffected by variations in cranberry juice. Focusing on the creature that has fused, the Gibbs free energy of adhesion changed into positive at a 27-weight percent concentration, indicating unfavourable adhesion. Adhesion of bacteria to each uroepithelial cell of E. coli HB101pDC1 was also evaluated for the mean-SD counts of bacteria for concentrations of 0, 5, 10, and 27 weight percent. were 50.2 per uroepithelial cell. [18]

It does see that a receptor with D-mannose or a mannose-like structure mediates the interaction between uropathogens and mucosal cells. This adhesion is inhibited by D-mannose and methyl g-Dmannopyranoside (AMM). N-acetyl-D-glucosamine, D-galactose and wheat Peanut and germ agglutinins don't have any influence. [19] AMM inhibition is reversible and dose-proportionate (between 2 and 6 mg) sugar/mL; at 25 mg, 100% inhibition takes place. sugar per milliliter. [64] Pre-attached E. coli can actually be removed from the mucosal attachment site cells by AMM and D-mannose. [19]

Pharmacokinetics:

The pharmacokinetic parameters of the different elements must be used to characterize the Cranberry plant's pharmacokinetics. Given that natural goods like cranberries contain literally hundreds of chemical elements, this task gets too much to handle. It is possible to identify the active moiety or moieties in order to reduce the options.

Eleven participants in good health took part in an investigation of the anthocyanidins excretion in the urine following consumption of a single 200 mL dosage of 651 mg of total anthocyanidins found in cranberry juice. Out of twelve anthocyanidins, six were also detected in the urine in cranberry juice, making up more than 90% of all anthocyanidins excreted in the urine. Cyanidin 3-O-galactoside = 3.7% and 14.3% of total urine anthocyanidins cyanidin 3-O-arabinoside = 12.0% of the dosage total anthocyanidins in the urine. [9]

Since cranberry juice contains salicylic acid, 22 healthy female volunteers were used to assess the pharmacokinetics of salicylate following cranberry consumption. For 14 days, 250 mL of cranberry juice was given three times a day (daily salicylate consumption = 5.25 mg as opposed to the typical dietary salicylate ingestion of 10–200 mg daily). The urine excretion of salicylic and salicylic acids was considerably raised within 1 week of commencement (both $p < 0.001$) and remained elevated at the end of the study (both $p < 0.001$) when compared to placebo in this crossover study. At the conclusion of the trial, the plasma salicylic acid concentration was considerably higher ($p < 0.05$), albeit with a minor absolute magnitude increase (baseline = 0.00138–0.00152 mg/dL - 0.00469–0.00276 mg/dL). [12]

65 healthy female volunteers, ages 19 to 28, were randomly assigned to receive either a placebo (n = 23), dried cranberry juice 400 mg once daily (n = 20), or dried cranberry juice 400 mg three times daily (n = 22) during the course of an 8-week trial. 200 mg of this dried product (Nutri-Cran 90) is equal to 5 g of fresh cranberries. A number of urine analytes, including hippuric acid, salicylic acid and its isomers, quercetin glucuronide isomers and dihydroxybenzoic acid isomers, increased significantly only in the 1200 mg/day group as compared to the placebo group (all $p < 0.05$). [20] The pharmacokinetics of flavonoids have been succinctly summarized in a recent review study. [4] Oral absorption of these substances is more effective when the natural glycosylated versions are used in contrast to the non-glycosylated agarose forms. The forms that are glycosylated compete with glucose for intestinal sodium/glucose transporter 1 (SGLT1) co-transporter. Just 5% of flavonoids consumed enter the bloodstream; the flavanol compounds are able to accomplish this with ease. Quercetin can be found in the glucuronidated or sulfated plasma forms. It is unknown where this happens (gut wall) as opposed to hepatic first-pass. Flavonoids are able to return to the intestinal passages across the transporter resistance to many drugs, the MRP-2 protein and they are removed from the circulation through MRP-3. Absent absorption of flavonoids in the intestines is exposed to microbiological deterioration within the colon. [21]

Pharmacodynamics:

- **Antimicrobial Activity:** The in vitro antimicrobial activity of cranberry against a wide variety of microorganisms. [29,36] In addition, the only single constituent of cranberry juice tested, 1-O-methylgalactose, was found not to have antibacterial activity. [11]

- **Inhibition of Adherence to Surfaces:** Adherence/anti-adherence activities of cranberry juice were examined in 145 bacterial isolates: 63 E. coli (31 non-urinary, 32 urinary), 32 Proteus spp. (23 non-urinary, 9 urinary) and 15 Klebsiella spp. (14 non-urinary, 1 urinary). Urinary isolates of Proteus species, P. aeruginosa and E. coli adhered to uroepithelial cells more than non-urinary isolates did, but the only one with statistical significance was E. coli. This disparity was three times as large. When eight isolates of bacteria were first incubated with the juice cocktail, adherence dropped off dramatically of eight isolates, seven of which had two adherent urinary 1/2 adherent urinary Proteus spp., 2/2 E. coli, 2/2 nonurinary E. coli and adherent urinary P. aeruginosa (all $p < 0.05$). Prior to incubation, the juice cocktail significantly decreased the adhesion of uroepithelial cells for just three isolates. One Proteus species, one E. coli and 1 P. aeruginosa. [22] A 1:2 dilution of the cocktail almost completely inhibited type I fimbriae-mediated adherence of eight E. coli strains. [23] Only trimers were active at low concentrations: epicatechin-(4b-6)-epicatechin-(4b-8,2b-0-7) and -epicatechin-(4b-8)-epicatechin at 0.6, 1.2 and 2.4 ng/mL and epicatechin-(4b-8)-epicatechin-(4b-8,2b-0-7)-epicatechin at 1.2 and 2.4 ng/ml. [14] Fructose, vitamin C and 1-O-methylgalactose, all constituents of cranberry juice, had minimal to no effect on in vitro adherence to mucosal surfaces. [11,25]

- **Inhibition of Biofilm Formation**: Cranberry prevents P. gingival and S. mutans, two oral infections, from forming biofilms. [29,30] Furthermore, concentrates of juice (in concentrations) of 0% as the reference, 12.5%, and 25% in artificial urine reduced the production of biofilms in a dose-dependent manner by two UPEC strains that are papC-positive, but in the just 25% of UPEC strains that are papC-negative formation was prevented by there was no discernible connection between the juice and focus on the growth of bacteria and the impact on the development of biofilms on inert surfaces. [31] Cranberry juice's impact on crystalline catheter-blocking proteus was examined using an in vitro model of the catheterized bladder and biofilms of mirabilis. Twenty-four healthy volunteers were randomly assigned to have one or two drinks. 500 milliliters of water or cranberries peel and juice were gathered for the following eight hours. P. mirabilis was then used to test these urine samples and fake urine. Clinically isolated NSMG from an encrusted catheter in the model that is used in vitro. Encrustation levels of calcium and magnesium on the catheters showed no discernible differences between the two experimental setups when 500 mL quantities were consumed. Encrustation was considerably lower in the water condition when 1000 mL was consumed as opposed to the cranberry juice condition ($p = 0.007$) in both circumstances. [32] According to early evidence, exposure to strawberries specifically suppresses the formation of biofilms. Biofilms generated through oral uropathogenic E. coli and other pathogens seem to be prone to inhibition, in contrast to those generated by obstructing a catheter, unlike P. mirabilis. [32]

- **Effects on Urine Composition:** Numerous studies have looked at how cranberries affect the content of urine in order to determine how they work to prevent UTIs and the possibility that it could cause nephrolithiasis as an adverse drug reaction (ADR). Neither single doses (100–305 g of fresh cranberries and 1200–4000 mL of cranberry juice cocktail) nor multiple-dose regimens cranberry solids [Cranactin] at a dose of 1200 mg per day for 22–54 g of fresh cranberries each day for up to 2.5 days Cranberry juice (1200–4000 mL/day) for three days combined for as long as six days produced a clinically meaningful impact on the pH of urine. [33,34] The titratable acidity was raised by 1200 mL (30%) and 1500 mL single dosages 100 g (9%), 150 g (5%) and 200 g (-7%) of cranberry juice cocktail and 4000 mL (77%) fresh cranberries, 250 g (2%) and 300–305 g (18%). [35-36] Corresponding rises in organic acids in cranberry juice were 22%, 29% and 26% combined with 23%, 32%, 35%, and 48% preferring cranberries that are fresh. [35-36] The increase in titratable acidity for multiple-dose regimens was two to four days. 25% of 1500 mL/day, 15% of 2000 mL/day and the daily amounts of 2500 mL (37%) and 4000 mL (-7%) of drink made with cranberries. [37] Daily hippuric acid excretion rose by 508% following consumption of fresh cranberries, 305 g. [36] Alkali reserve in blood decreases of 20%, 45% and 63% following a single 100, 200 and 300 grams of fresh cranberries. [38] Cranberry juice, 400 mg; Cranactin pills three times a day for the mean urine surface tension rose by 2.5 days (11.5% in contrast to the average growth of 8.0%) with the addition of water.

Table 2: in- vitro antimicrobial activity of cranberry

Study (year)	Preparations and test conditions	Micro-organisms	Results
Gupta et al. [24] (2007)	juice concentrate in synthetic urine (0%,12.5%,25%)	upec (2 papc-positive,1 papc-negative strains)	5% and 25% dilutions produced statistically similar growth inhibition against all 3 strains. No significant relationship between effect of juice concentrate on bacterial growth and effect on biofilm formation on surfaces.
Sobota [25] (1984)	freshly prepared juice in culture medium (33%)	escherichia coli (134 unselected clinical isolates)	no effect on growth
Cavanagh et al. [26] (2003)	juice diluted 1:5 with culture media (16.7%)	12 strains (university of new south wales, australia collection): *alcaligenes faecalis* *e. coli* *mycobacterium phlei* *s. aureus* *p. aeruginosa* *mrsa* *salmonella typhi* *salmonella california* *shigella sonnie* *e. faecalis* *s. enteritidis*	degrees of growth inhibition 100% 92% 100% 84% 75% 100% 75% 25% 100% 100% 25%

Valent ova et al. [27] (2007)	dried cranberry juice powder (200mg=5g fresh cranberries) used in standard microdilution plate mic methodology	variety of hospital isolates (staphylococcus aureus, mrsa, vr enterococcus faecium, klebsiella pneumoniae.)	virtually nil activity (mics 179-357mg/ml) [p. aeruginosa most susceptible]
Lee et al. [28] (2000)	5-fold-concentrated preparation of juice (to stimulate concentrate) in culture medium (50%)	7 atcc strains: e. coli atcc 29522 s. aureus atcc 29213 pseudomonas aeruginosa atcc 27853 enterococcus faecalis atcc 29212 k. pneumoniae atcc 13883, etc.	5/7 strains had no growth at 24 h while e. faecalis and s. enteritidis had reduced counts compared with unsupplemented media. Some activity noted in dilutions as high as 1:32

Clinical Efficacy:

Every clinical finding that will be covered in this article relates to the effectiveness of cranberry products in preventing UTIs, as determined by clinical findings regarding the outcomes of laboratory tests (leukocytes, bacterial counts, nitrites, and leukocyte esterase). No published information about the use of cranberry products by themselves or in combination with results of using antimicrobials to treat UTIs of an unreleased investigation on the management of 6 patients using 12 pills a day for UTIs 800 mg/capsule of cranberry juice concentrate (Pharma caps brand) showed no signs of recovery. [39] In the same trial, 20 participants who followed the same prophylactic regimen as 21 did not have UTI subjects (95%). [39]

- **Prophylaxis in Adults:** Overall, tolerance and efficacy have been characterized as good, with sporadic reports of gastrointestinal distress and the requirement for higher insulin dosage in individuals with diabetes 3 female kidney transplant recipients patients with an average of 3 to 5 hard-to-treat UTIs per year experienced significant drops in incidence of UTIs (to 0–1 incident per year) following starting a prophylactic cranberry regimen. Relentless E. coli, Proteus species, Klebsiella-caused bacteriuria spp. and more organisms were unable to be eliminated by using items made from cranberries. In general, cranberry products should not be administered to individuals who have ileal channels as a result of unbearable irritation of the urostomal mucosa. [40]

- **Prophylaxis in Children's:** Well as the epidemiology of infections (overall, respiratory, enteric). Subjects were randomized to receive either cranberry juice cocktail 1.67 mL/kg/day (maximum 300 mL/day) [n = 171] or placebo (n = 170) for 3 months. The major reasons for premature discontinuation were refusal to drink the beverage (6 placebo/4 cranberry), parents became tired of the study (3/7), rash (1/0), gastric symptoms (0/2), illness during the trial (1/2), and unknown (0/3). There were no significant intra- or intergroup differences in the nasopharyngeal carriage of respiratory pathogens. As measured by bacterial fatty acid composition, fecal flora significantly changed in both groups over time (both $p < 0.001$), but the intergroup differences were not significant. Similar findings were noted for frequencies of possible bacterial and viral infections and three of the four most common pediatric infections. Only for conjunctivitis was there a significant intergroup difference of 0.1 and 0.4 diagnoses per person-year at risk in the placebo and cranberry groups, respectively ($p = 0.05$). Thus, the cranberry juice cocktail was well tolerated and did not affect bacterial colonization and infection epidemiology in a pediatric population. [41]

- **Meta-Analyse:** In general, clinical trials have been of low quality; randomization systems have been weak or uneven and groups have been small. The majority don't have a power analysis to compute sample size to prevent the statistical error known as type 2 (false negative). Research has shown that too short a time frame (less than six months). Research has not objectively evaluated treatment compliance (e.g., by measuring urine output of proanthocyanidins or more distinct indicators of cranberry). The rates of withdrawal have been as high as 47 percent. Kids in particular have mentioned the flavour of the juice as the primary cause of therapeutic discontinuation. [42]

Table: 3 clinical trials of cranberry products in the prevention of urinary tract infection (UTI) or colonization in adults and children

Study (year) and design	Population (no.)	Treatment	Results
women with UTIs			
Walker et al. [43] (1997) r, db, pc, co	women with recurring UTI aged 28-44y (19)	400mg cranberry solids capsule [a] od * 3mo and placebo * 3mo. order of treatments was randomized 6mo study duration (no wash out period between phases)	10 completed study (9 withdrew because of pregnancy, non-urinary infections requiring therapy, loss to follow-up).21 UTIs occurred during the study in these 10 sub. only 2/21 UTIs (10%) were due to non-Escherichia coli bacteria.
patients with neurological disease			
Mcguinness et al. [44] (2002) r, db, pc	patients with neurogenic bladder (135) [d]	8000mg cranberry supplement capsule [e] od.placebo od. 6mo study duration	12 sub. did not complete study participation. 34.6% of cranberry and 32.4% of placebo recipients developed a UTI during study (p = ns).

Tolerability:

65 healthy participants participated in an 8-week study of the effects of consuming 400 and 1200 mg daily of dried cranberry juice on the makeup of urine, 57 participants finished the evaluation. Six patients and two placebo recipients had premature cessation due to adverse drug reactions. About 1200 milligrams per day of dried cranberries. The acidity in the stomach and frequent urination were among the factors that caused the latter group to stop. Every biochemical alteration in each of the three groups was in line with physiological fluctuation. [27] Concerns have been raised over the possibility of nephrolithiasis during therapy. This toxicity has been assessed in four investigations potential. Twelve healthy male volunteers, ages 18 to 38, were given a typical diet in one study and received treatment using four 5-day regimens in a row: 330 mL of water (placebo) every day, plum juice, blackcurrant juice and cranberry juice. When comparing cranberry juice to a placebo, urinary pH decreased, oxalic acid production increased and uric acid relative saturation increased (all $0.01 < p < 0.05$). When blackcurrant juice was used instead of a placebo, the pH increased and increased both oxalic acid production ($0.001 < p < 0.01$) and citric acid ($p < 0.05$; $0.01 < p$). No urine parameter was significantly impacted by plum juice. It was concluded the potential involvement of blackcurrant juice when urate nephrolithiasis is being treated is due to its alkalinizing

properties. Cranberry juice could increase the chance of urate stones but could also function in the management of brushite, apatite and nephrolithiasis due to struvite. [45]

According to a comprehensive analysis of the literature, there is no concrete proof that eating cranberries during pregnancy poses any risks to the mother or foetus. [46] Indirectly, there is solid scientific evidence that supports that cranberry might not be so dangerous. [47] Cranberry juice's safety or damage during lactation is unknown. [46] Five healthy volunteers, two of whom were female, were treated for seven days at the manufacturer's facility in the fourth trial to assess the impact of cranberry concentrate tablets on urinary risk factors for nephrolithiasis suggested dosage. Urine samples were taken every 24 hours at baseline and on the day of the study. When the seven-day cranberry program is over, the only notable variations between baseline and urinary oxalate were used as part of the post-cranberry treatment. Sodium output (increased mean 43.4%; $p = 0.01$) ($p = 0.03$), magnesium output (increased mean 41%, $p = 0.02$), potassium production (rose), mean 47.3% calcium oxalate supersaturation (raised mean 50.7%; $p = 0.03$) and calcium oxalate mean 67.5%; $p = 0.006$). Consequently, when two people took cranberry concentrate tablets, their urine output significantly increased. possible lithogenic substances (sodium, oxalate) and two substances that prevent the development of stones (magnesium, potassium). In this study, cranberry concentrate was found to possibly enhance the risk of oxalate stones. [48]

Drug Interactions:

Flavonoids, which are major constituents in cranberries, have well-known effects on cytochrome P450 (CYP) drug-metabolizing enzymes. They can induce the biosynthesis of several CYP isoenzymes, inhibit or stimulate the enzymatic activities of CYP isoenzymes and are metabolized by several CYP isoenzymes. Table 4 illustrates flavonoids and their effects on various CYP isoenzymes. For example, flavanone and flavone enhance the activities of glutathione-S-transferase and uridine diphosphate-glucuronosyl-transferase, while quercetin and tangeretin do not. Some resemble the estrogen in structure and can have estrogenic or antiestrogenic activities (most natural flavonoids are not potent in these activities). [49] Dietary flavonoids are broken down by the intestinal flora (glycosides are broken down to release flavonoids or aglycones), which are then absorbed phase I oxidation occurs when flavonoids undergo hydroxylation and demethylation as they transit through the liver and CYP isoenzyme-mediated. Following that, these metabolites undergo conjugation, which includes O-methylation, sulfation and glutaronidation. The gut facilitates the breakdown of the flavonoid skeleton by the ring scission of bacteria. A few instances of flavonoid metabolism include:

- *Galanin, kaempferol, and quercetin (mediated primarily by CYP 1A1)*
- *Genistein or obol (mediated by CYP isoenzymes 1A1, 1A2, 1B1, 2E1).*

Of interest, naringenin is not metabolized via any CYP isoenzyme. [49] In vitro, 2.5% tea, 2.5% grape juice (Welch's 100% pure juice), 2.5% cranberry juice (Ocean Spray cranberry juice cocktail, 27% pure juice), 2.5% cranberry juice placebo and 2.5 mmol/L sulfaphenazole reduced flurbiprofen hydroxylation to (mean – SD) 11%–8%, 10%–7%, 56%–16%, 85%–5%, and 21%–6% of control, respectively (all $p < 0.01$) prior to morning flurbiprofen administration. Only fluconazole exerted a significant effect on flurbiprofen pharmacokinetics, with increases in Cmax, elimination half-life (t1 = 2) and AUC (area under curve), and a decrease in apparent oral clearance (all $p < 0.05$). [50]

Table 4: activities of flavonoids on cytochrome p450 (cyp) isoenzymes [49]

CYP isoenzyme type	Type of activity agonist/inducer	Antagonist	No effect
1a1	quercetin galangin diosmin diosmetin tangeretin	quercetin kaempferol galangin	genistein equol prenylchalcones prenylflavanones
1a2	flavone tangeretin		genistein equol
2b1/2b2	flavonone (flavone) (tangeretin)		
3a4	flavone tangeretin	nanringenin bergamottin flavolignan sylimarin biapigenin hyperforin	

A three-way crossover trial that was randomized, placebo-controlled and had twelve healthy male volunteers examined the impact of cranberry juice and pomelo juice on the pharmacokinetics of oral ciclosporin. Participants were given a single oral dose of 100 mg dosages three times (with 240 milliliters of water control), cranberry and pomelo juice with washout intervals of two weeks. Juice from pomelo was made with cranberry juice and fruit was acquired by reassembling frozen ocean spray focuses on every day of administration. Co-administration of pomelo juice produced shows notable rises in the average whole blood ciclosporin AUC (both from zero to the final measurable drug concentration and Cmax by 19.4%, 18.9%, and 12.1% and infinity ($p = 0.0001$, $p = 0.0001$ and $p = 0.0167$, respectively). Only the rise in AUC, though, could be regarded as therapeutically important. These findings were in line with increased bioavailability because to CYP3A4 and P-glycoprotein inhibition within the intestinal wall. Cranberry coadministration juice produced a statistically significant (albeit not clinically meaningful) average 6.6% decrease in AUC ($p = 0.0054$). [51]

Dose Administration:

The recommended dosage of cranberry products for preventing UTIs has not been clearly established. Among the things that are offered are drinks and a hefty dosage of dried cranberry extract formulas. The beverage that has been studied for the best formulations is ocean spray, a sweetened cranberry juice drink that makes up around 25% of pure juice. Suggested dosages have varied from 4 to 32 every day (three separate dosages) together with meals every day. [52, 53] Suggested dosages for the concentrated dried juice extract (in pill form) range between 600 and more than 1200 mg per day (in split portions twice or three times every day). [52, 53] One significant potential risk associated with the capsule formulations is the dried cranberry's sensitivity extract contents for degradation through exposure to light, heat and cold, but the inclusion of E and C vitamins has a stabilizing effect. [54] Cranberries items at this dose are costly (2008 costings over $1000 USD per year) and unlikely to be covered by a prescription medication benefit plan because of their designation as either dietary items or nutritional supplements. [54]

Benefit's:

1. **Fighting age-related damage:**

- Cancer
- Diabetes
- Heart disease
- Digestive health
- Urinary tract health. [55]

2. **Improving heart health:** Polyphenols, which are abundant in cranberries, may help protect the heart. In 2011, cranberry juice was discovered to raise the levels of antioxidants in the blood plasma of females with metabolic syndrome. Cranberry juice drinkers also exhibited decreased levels of low-density lipoprotein (LDL). The "bad" kind of cholesterol is LDL. [55]
3. **Treating or preventing urinary tract infection (UTI):** The reduction of UTI incidence is thought to be due to the ability of antibacterial properties to reduce the colonization of *Escherichia coli in* the bladder. The bacteria, which is known better as *E. coli* is the cause of most UTIs. [55]
4. **Preventing infections:** Cranberries inhibited the growth of seven bacterial microbes. The study did not assess whether cranberries or cranberry juice could prevent infection with these microbes in humans. [55]

Conclusions:

Over many years, cranberry has been well studied in relation to the treatment of UTIs. There is currently no proof that cranberries can be used to treat urinary tract infections. Thus, the emphasis has been on using it as a prophylactic measure. Both in vitro and in vivo, cranberry has shown promise in animals to prevent urinary tract infections. It seems to function by preventing the P-fimbriated pathogens (such as E. coli, which is uropathogenic), thereby hindering colonization and the uroepithelium later infection. With this activity, the cranberry component or components have been isolated, a difficult undertaking given the hundreds of substances present in the fruit and its juice. Based on reasonable evidence, it appears likely the moieties of anthocyanidin and proanthocyanidin are strong antiadhesion substances. Nevertheless, there are still issues with cranberry product standardization, which makes it very challenging to evaluate goods or draw conclusions. Regretfully, the majority of clinical trials have been difficult various flaws in the design and nobody has assessed certain important chemicals produced from cranberries that are thought to be active moieties (e.g., proanthocyanidins). Overall, the effectiveness of prevention of cranberries has been inconsistent and low at best. It has been determined by meta-analyses that recurrence rates decrease by around 35% of women in their early to middle years. The effectiveness of cranberries in different demographics, such as the elderly, is dubious for pediatric patients, those with neurogenic bladders and those with long-term indwelling urinary catheters. Clinical trials that are ongoing Include a randomized controlled study comparing cotrimoxazole with cranberries for the prevention of UTIs. In women who are not yet menopausal and a randomized, controlled experiment with a range of doses of products containing cranberries in the prevention of recurrent UTIs in women. [56,57] The significant withdrawal rates (up to 55%) indicate that these products might not be long-term acceptable intervals. Among the adverse effects are gastrointestinal intolerance and gaining weight (because of the excessive caloric load) and reactions between drugs and cranberries because of flavonoids ability to suppress CYP-mediated drug metabolism.

The results of the Cochrane collaboration endorse the possible application use of cranberry products to prevent recurring UTIs in women in their youth and middle years.[57]

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