Cranberry SAP-UTI

Science-based cranberry (whole berry) concentrate for UTI prevention

Native to North America, cranberries have been used as a medicinal agent for centuries. Cranberries contain proanthocyanidins, which have been shown to inhibit the fimbrial adhesion of bacteria, including *Escherichia coli*, to the urinary tract epithelium, hence preventing bacterial proliferation and infection. These unique proanthocyanidin compounds, and not acidification of the urine, are suggested to be pivotal in preventing urinary tract infections (UTIs).

ACTIVE INGREDIENTS

Each non-GMO vegetable capsule contains:

Cranberry (*Vaccinium macrocarpon*) . . . . . 600 mg

Providing:

Proanthocyanidins . . . . . 27 mg

From 100% ripe red cranberries (*Vaccinium macrocarpon*)

Other ingredients: Vegetable capsule composed of vegetable carbohydrate gum and purified water.

This product is non-GMO and vegan friendly.

Contains no: Gluten, soy, wheat, corn, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, or sugar.

Cranberry SAP-UTI (concentrate) contains 60 vegetable capsules per bottle.

DIRECTIONS FOR USE

Adults: Take 2 capsules daily or as directed by your healthcare practitioner.

2 capsules provide 54 mg of proanthocyanidins.

INDICATIONS

Cranberry SAP-UTI supplies a minimum daily dose of approximately 54 mg of proanthocyanidins from whole cranberry extract that can help:

- Prevent recurrent UTIs in women
- Improve cardiovascular health and support weight management
- Support immune function and immune system

NATURAL SYNERGISTIC BLEND

Cranberries contain a diverse range of phytochemicals. **Cranberry SAP-UTI** is manufactured from whole ripe red cranberries containing the berry's natural blend of antioxidants and other phytonutrients. The synergy of the complex phytonutrient blend provides increased bioavailability and protective health benefits.

PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for each **Cranberry SAP-UTI** lot number have been tested by an ISO 17025–accredited third-party laboratory for identity, potency, and purity.

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

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CRANBERRIES AND PROANTHOCYANIDINS

Cranberries or *Vaccinium macrocarpon* are one of three fruits native to North America and have been used as a medicinal agent by Native Americans for centuries.[1, 2] The single strength juice extracted from cranberries is highly acidic (pH 2.5), astringent and quite unpalatable.

Cranberries contain a wide variety of diverse compounds which are responsible for the fruits' biological effects.[3] Cranberries supply a rich phytonutrient blend containing anthocyanidins, proanthocyanidins, flavonol glycosides, sugars, organic acids and phenolic acids.

Proanthocyanidins are a group of condensed tannins (polyphenolic compounds) that have been isolated from cranberry fruit and that are believed to be responsible for the health benefits associated with cranberry intake.[4] Specifically, increased dietary consumption of cranberry products has been associated with a reduced risk of urinary tract infection (UTI) and maintenance of urinary tract health.[1, 2, 4–7]

URINARY TRACT INFECTIONS (UTIs)

Urinary tract infection is defined by the presence of microorganisms in the urinary tract, including the bladder, prostate, collecting system and kidneys.[2] Annually, UTIs are responsible for more than 11 million physician visits in the United States.[5]

UTIs have a high resistance to first-line antibiotic therapy,[5] and treatment with antibiotics is associated with side effects such as nausea, diarrhea, and *Candida* infections.[6]

UTIs are approximately 50 times more prevalent in adult women than adult men; however, UTIs can occur in men, women and children.[7] It has been estimated that 30% of women will experience at least one UTI during their lifetime,[7] and of these women, 25% will experience frequent recurrent infections.[8]

Women are most susceptible to UTIs because they have a short urethra that allows for bacteria to easily ascend into the bladder.[7] Pregnancy, sexual activity, aging, and use of urogenital medical devices (i.e. catheters) increase the risk and severity of UTIs. Symptoms of UTIs include frequent and urgent need to urinate, cloudy urine, painful urination, and lower-back pain.[2]

MECHANISMS OF ACTION

Acidification of the Urine?

Cranberries are very acidic, containing quinic acid, malic acid and citric acid.[1, 3, 7] Early research observed that cranberry quinic acid produced large amounts of hippuric acid, a strong antibacterial agent excreted in the urine.[1, 4, 7]

For years, researchers believed that the bacteriostatic effect of cranberry consumption was related to the acidification of urine; however, several studies failed to confirm this hypothesis, as consumption of cranberries only produced very slight increases in urinary acidity, and did not alter antibacterial activity in the urinary tract.[1, 2] Due to a lack of scientific substantiation, urinary acidification is no longer believed to be the mechanism responsible for the action of cranberry on UTIs.[1, 4]

Antiadherence

UTIs are most often caused by uropathogenic bacteria that are harbored in the colon and ascend up the urinary tract, adhere to mucosal surfaces, proliferate, and cause infection.[4] The most common urinary pathogen, accounting for 85% of UTIs, is *Escherichia coli*.[2]

The bacterial cell wall of *E. coli* contains protein-like fibres called fimbriae that readily attach to uroepithelial cells.[9] *E. coli* fimbriae produce two fimbrial adhesions: type 1 (mannose-sensitive) and P-type (mannose-resistant).[1, 9] It is the adherence of bacteria (*E. coli*) to uroepithelial cells that is the critical step in the development of UTIs.[9]

Cranberries contain two anti-adhesion compounds: fructose and proanthocyanidins.[1, 4, 9] While fructose inhibits type 1 fimbrial *E. coli* adhesion, proanthocyanidins competitively inhibit P-type fimbrial adhesion and proliferation, resulting in an increased excretion of *E. coli* in the urine.

To date, there is substantial in vitro and in vivo evidence showing that proanthocyanidins effectively inhibit P-type *E. coli* from adhering to uroepithelial cells[4, 9] from 2 to 10 hours after ingesting cranberries.[1] However, since proanthocyanidins are more effective at preventing bacterial adherence than displacing adhered bacteria from uroepithelial cells, cranberry consumption is indicated for prevention rather than treatment of UTIs.[1, 6]

CRANBERRIES, UTIs, AND NUTRITION RESEARCH

Randomized intervention trials have observed a clinical benefit of cranberry products in preventing UTIs.[1, 10–13]

Scientific evidence reports that sexually active women with recurrent UTIs show greatest benefit from the preventative effects of cranberry intake, with an associated 50% reduction in UTI disease morbidity.[1]

Furthermore, evidence from a randomized clinical trial on elderly women reported a significant reduction in bacteria and exudate found in the urine after cranberry juice intake.[13]

An epidemiological study on first-time UTIs and sexual behaviors found that regular consumption of cranberry juice was associated with a decreased risk of UTIs.[14]

As compared to the preventive effect of cranberry in UTIs, there are no scientific studies evaluating the effectiveness of cranberry products in the treatment of UTIs.[1, 7] More scientific evidence is needed to confirm the provocative findings obtained to date.

SAFETY OF CRANBERRIES

Intake of cranberries is considered to be safe.[1] However, high intakes of cranberry juice may have a laxative effect.[1] Cranberries contain moderately high levels of oxalate, and Terris et al.[15] reported that patients at risk of nephrolithiasis (kidney/urinary stones) should avoid dietary supplementation of cranberries.

In 2004, the Committee on Safety of Medicines warned health professionals about the possibility of interaction between warfarin and cranberry juice.[16] However, it is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin, though similar caution should be considered. Currently, there is not enough information available to assess the interaction of cranberry intake with the use of dietary supplements and medications.

ACCEPTABILITY OF CRANBERRY PRODUCTS

Cranberry juice cocktail, a sweetened, high-calorie beverage containing about 27–33% cranberry juice, is the most common form of cranberry consumption.[1, 2] However, due to the high patient-dropout rates in clinical studies associated with intolerance of long-term cranberry juice intake, cranberry capsules may be better tolerated.[1]

Moreover, a study conducted by Strothers[9] found that cranberry tablets are more cost-effective than organic cranberry juice. Therefore, having similar clinical results, taking cranberry supplements (capsules or tablets) may be a better alternative to drinking cranberry juice for the prevention of UTIs.

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INDICATION-SPECIFIC DOSAGE SUMMARY BASED ON HUMAN CLINICAL RESEARCH#

#Please note these suggestions are guidelines based on the clinical studies. Evidence for efficacy and safety has been qualitatively (study quality in terms of study design, sample size, appropriate methods of analysis, use of appropriate placebo/control, bias etc.) assessed and has been rated using a 5-star ★ rating classification.

Indication	Suggested Cranberry SAP dosage	Supporting evidence and study outcomes	Study design	Outcomes measures	Safety	Evidence quality rating
WOMEN HEALTH						
Premenopausal UTIs[1]	2 capsules/day	A significant decline in the recurrence of UTIs and their duration in the intervention group. A substantial number of subjects had 0 UTI recurrence, and a significant difference in the onset of the first UTI.	Randomized, double-blind, placebo-controlled pilot study (*n* = 115; 26 weeks). Cranberry extract with 36 mg of cranberry PACs (proanthocyanidins) per day. > 5 × 10^8 CFU/capsule of *Lactobacillus acidophilus* PXN 35 and *Lactobacillus plantarum* PXN 47.	Screening by urinalysis and culture; recording UTI symptoms, including dysuria, urinary frequency, urgency, suprapubic pain, and hematuria.	No severe adverse effects reported (abdominal distention and diarrhea).	★★★
Recurrent UTI[2]	1 to 4 capsules/day	Significant reduction in recurrence of UTIs.	7 randomized controlled studies (*n* = 1498; 6 to 12 months). 7.5 g of cranberry concentrate or 120 to 480 ml of cranberry juice or 500 mg of cranberry extract powder per day, with 2.8 mg to 224 mg of cranberry PACs per day.	Risk of UTI recurrence.	No severe adverse effects reported (gastrointestinal disturbance).	★★★★
Antiadhesion[3]	2 capsules/day	Significant decline in bacterial adhesiveness in the intervention group.	Randomized, double-blind, cross-over, placebo-controlled study (*n* = 24; 1 week). 120 mg of cranberry extract with 36 mg of PACs per day + 60 mg of ascorbic acid.	Bacterial strain examination, *E. coli* ATCC 25922, *E. coli* ATCC 35218, bacterial adhesion index.	No severe adverse effects reported.	★★★★
CARDIOVASCULAR AND METABOLIC HEALTH						
Cardiovascular health[4],[5],[6]	1 capsule/day	Significant drop in total cholesterol and triglycerides levels in the intervention group; also, a substantial decline in mean insulin and HOMA-IR levels.	Randomized, triple-blind, placebo-controlled, parallel-designed study (*n* = 110; 6 months). 144 mg/d of cranberry.	Lipid profile, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), glycemic measurements [fasting blood sugar (FBS) and insulin level].	No severe adverse effects reported.	★★★★
	2 capsules/day	Significant improvement of large LDL particles and LDL size in the intervention group; also, a substantial increase in HDL global efflux. A significant effect on total cholesterol, HDL-C, non–HDL-C, and glucose.	Randomized, double-blind, placebo-controlled, 2-period crossover study (*n* = 40; 8 weeks). 500 ml/d of cranberry juice.	Central systolic blood pressure or central or brachial diastolic pressure, TC, TG, HDL-C, LDL-C, glucose, serum high-sensitivity C-reactive protein (CRP), and serum HDL.	No severe adverse effects reported.	★★★★

	4 capsules/day	Significant decline in fasting serum triglycerides; also, a substantial decrease in CRP, fasting plasma glucose, and diastolic BP.	Randomized, double-blind, placebo-controlled, parallel-arm study (*n* = 56; 8 weeks). 480 ml/d of low-calorie cranberry juice (LCCJ) with 118 mg of PACs.	Blood glucose, serum total, HDL, LDL cholesterol, TG concentrations, serum insulin concentration, HOMA-β, and CRP.	No severe adverse effects reported.	★★★
Obesity [7],[8],[9]	4–5 capsules/day	Significant decline in 8-isoprostane, indicating decreased lipid peroxidation; also, a substantial difference in TAG levels and nitrate levels.	Randomized, double-blind, placebo-controlled, parallel-designed pilot study (*n* = 35; 8 weeks). 450 ml/d of low-calorie cranberry juice (LCCJ) with 143.6 mg of PACs.	Changes in insulin sensitivity and cardiovascular risk factors, including vascular reactivity, blood pressure, RMR, glucose tolerance, lipid profiles, and oxidative-stress biomarkers.	No severe adverse effects reported (diarrhea, phlebitis, weight loss).	★★★
	2 capsules/day	Significant decrease in LDL-C and total:HDL cholesterol ratio; also, a substantial reduction in LDL-C and cholesterol levels.	Randomized, double-blind, placebo-controlled study. (*n* = 30; 12 weeks). 500 mg/d of cranberry extract powder.	Changes in lipid profiles, oxidized low-density lipoprotein (ox-LDL), glycemic control, components of the metabolic syndrome, C-reactive protein (CRP), and urinary albumin excretion (UAE).	No severe adverse effects reported.	★★★
	2 capsules/day	Significant drop in MMP-9 levels; also, a significant decrease in plasma nitrites/nitrates (NOx) levels and circulating apoAI levels.	Pilot study (*n* = 30; 12 weeks). Low-calorie cranberry juice cocktail (weeks 1–4: 125 ml/d, weeks 5–8: 250 ml/d, and weeks 9–12: 500 ml/d).	Anthropometric indices, blood pressure, TC, TG, HDL-C, LDL-C, VLDL-C, MMP-9 levels, and NOx concentrations.	No severe adverse effects reported.	★★
URINARY HEALTH						
Recurrent UTI [10],[11],[12],[13]	2 capsules/day	Significant decline in the number of bacterial growth, mannose-resistant hemagglutination assay (MRHA), and bacterial adhesion.	Randomized, placebo-controlled, prospective study (*n* = 72; 12 weeks). 60 mg/d of PACs.	Change or reduction in the recurrence of UTI, MRHA, detecting biofilm formation on urinary catheters.	No severe adverse effects reported (constipation).	★★
	1 capsule/day	Significant reduction in the recurrence of UTI; also, a substantial decline in the mean duration of UTI and need for medical consultation.	Placebo-controlled, pilot study (*n* = 44; 2 months). 20 mg/d of cranberry extract with 36 mg of PACs.	Comparison of the number of UTIs, number of symptom-free subjects, duration of UTI episodes and the need for medical attention; normal urinalysis.	No severe adverse effects reported.	★★
	1 capsule/day	Significant decline in the mean number of UTIs in the intervention group, and a substantial number of patients receiving cranberry were symptom-free.	Placebo-controlled, pilot study (*n* = 36; 2 months). 20 mg/d of cranberry extract with 36 mg of PACs.	Number of UTIs, number of symptom-free subjects.	No severe adverse effects reported.	★★
	1 capsule/day	Significant decline in the mean number of UTIs in the intervention group; also, a substantial drop in the UTI reported to the registry.	Pilot, registry study (*n* = 43; 60 days). 20 mg/d of cranberry extract with 36 mg of PACs.	Number of UTIs, number of symptom-free subjects.	No severe adverse effects reported.	★★

IMMUNOLOGICAL HEALTH

Antiadhesion activity [14], [15], [16]	1 capsule/day	Pilot study showed a significant ex vivo antiadhesion activity in both study groups, and the clinical study showed substantial antiadhesion activity in both study groups.	**Study 1:** Randomized, double-blind, placebo-controlled pilot study (*n* = 10; 1 week). 450 ml/d of cranberry extract beverage (CEB) or a cranberry extract and juice beverage (CEJB) with 4.4 mg and 5.7 mg of PACs. **Study 2:** Randomized, double-blind, placebo-controlled, crossover study (*n* = 59; 1 week). 450 ml/d of CEJB or 240 ml/d of low-calorie cranberry juice cocktail (LCJC) with 6.8 mg and 4.6 mg of PACs.	Assessment of assess antiadhesion activity by hemagglutination assay.	No severe adverse effects reported.	★★
	8 capsules/day	Significantly increase in urinary antiadhesion activity against P-type *E. coli*; also, substantial ex vivo antiadhesion effects on type 1 *E. coli*.	Randomized, double-blind, placebo-controlled, crossover, pilot study (*n* = 20; 36 hours + 7-day run-in period). 18 g/d of cranberry chew with 240 mg of PACs.	Urinary antiadhesion activity against P-fimbriated *E. coli*, urinary antiadhesion activity against type 1 *E. coli*.	No severe adverse effects reported.	★★★
	2 capsules/day	Significant antiadhesion activity against fimbriated *E. coli* in all three test product-receiving participants.	Randomized, double-blind, placebo-controlled, ex vivo, acute, crossover study (*n* = 20; 36 hours + 7-day run-in period). 500 mg/d of cranberry extract (3 different test products) with 36 mg of PACs.	Measurement of antiadhesion activity against P-fimbriated *E. coli* of urinary samples.	No severe adverse effects reported.	★★★
Antiinflammation [17]	2 capsules/day	Significant changes in interferon-γ levels indicating anti-inflammatory effects; also, a substantial decrease in endothelin-1 and elevated nitric oxide and the reduced:oxidized glutathione ratio, fasting CRP, and serum insulin levels.	Randomized, double-blind, placebo-controlled, parallel design study (*n* = 78; 8 weeks). 450 ml of low-calorie, high-polyphenol cranberry extract beverage (CEB).	Oxidative stress and inflammation biomarkers assessment, lipid metabolism parameters, glucoregulation, and polyphenol status.	No severe adverse effects reported.	★★★

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