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Cranberry juice – a well-characterized folk-remedy against bacterial urinary tract infection

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Cranberrysaft – ein gut untersuchtes Heilmittel bei bakteriellen Harnwegsinfektionen

Zusammenfassung. Die Cranberry (Vaccinium macrocarpon) ist in Nord-Amerika ein traditionelles Heilmittel bei Infektionserkrankungen. Seiner Wirksamkeit liegt ein gut charakterisierter anti-Adhäsionsmechanismus durch Cranberrry-Proanthozyanidine zugrunde, der die feste Andockung von Bakterien im Gewebe verhindert. Dieses Wirkprinzip ist im menschlichen Urin nach Trinken von Cranberrysaft nachweisbar. Cranberrysaft und -extrakte zur Prophylaxe von Harnwegsinfektionen bei Frauen sind durch klinische Studien untersucht und gelten als evidenzbasierte Strategie. Die anti-Adhäsionswirkung der Cranberry-Proanthozyanidine wird derzeit auch bei weiteren bakteriell verursachten Erkrankungen wie Karies/Parodontose und Helicobacter pylori-assoziierte Gastritis untersucht.

Schlüsselwörter: Cranberry, anti-Adhäsionswirkung, Proanthozyanidine, Karies, Parodontose, Helicobacter pylori, Anti-oxidanzien.

Summary. Cranberry (Vaccinium macrocarpon) is a North-American folk remedy for treating and preventing infection. Research has identified an anti-adhesive mechanism of cranberry-proanthocyanidins that inhibit docking of bacteria on tissues "in vitro". This efficacy mechanism can be traced in the patient's urine following oral intake of cranberry juice. The efficacy of cranberry juice and extracts as a prophylactic agent against recurrent urinary infections is well documented in women. The anti-adhesion effect of cranberry-proanthocyandins can also be applied for treatment of other common diseases of bacterial pathogenesis, e. g. Helicobacter pylori-associated gastritis and dental caries/periodontal disease.

Key words: Cranberry, anti-adhesive effect, proanthocyanidins, caries, periodontal disease, Helicobacter pylori-associated, gastritis.

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Urinary tract infection

Urinary tract infections (UTI) have a high incidence worldwide and a substantial share of the public health budget is spent on their treatment. UTI confined to the lower urinary tract are comparatively harmless. Ascending UTI may cause renal parenchymal damage, leading eventually to renal failure. Every second woman suffers from bacterial UTI at least once in her life, and recurrent UTI occur in about 25% of elderly women.

The bacterium *Escherichia coli* (*E. coli*) causes most uncomplicated UTI. In complicated upper UTI, E. coli strains of specific uro-pathogenic virulence predominate. Urovirulence is strongly defined by bacterial fimbriae, which mediate the firm adherance to the host's tissue. Adhesion is accomplished by binding of lectins exposed on the surface of these fimbriae to complementary carbohydrates of the host tissue [1].

Fimbrial adhesion is a key-event in UTI following bacterial colonisation of the host tissue. Adhesion is therefore a promising target for therapeutic intervention.

When adhesion is mediated by type-1 fimbriae which are standard equipment of E. coli, it is inhibitable by fructose (hence mannose-sensible fimbriae). The more vicious E. coli isolates from patients with pyelonephritis and recurrent UTI, bear further types of fimbriae, notably p-fimbriae. P-fimbriae are associated with the alpha-Gal [1–4] beta-Gal specific lectin, a marker of pathogenicity. The prefix "p" is derived from pyelonephritis, and binding of p-fimbriated E. coli to glycosphingolipids of the lipid-double-membrane of renal cells precedes renal parenchymal invasion. P-fimbriated E. coli overrun the kidney's immunological defense lines by impairing synthesis and secretion of urinary IgA through inhibition of the polymeric Ig-Receptor on renal epithelia [2]. Adhe-

Table 1. Anti-adhesive activity of urine from volunteers after cranberry juice ingestion in comparison with placebo on adhesion of 6 different *E. coli* strains to uroepithelial cells (mean values from 20 volunteers) [13]

Regimen	Adhesion-*index*	Reduction of bacterial adhesion (%)	P Student's T-Test
250 ml placebo + 500 ml water	7.04 ± 5.9	–	–
750 ml placebo	6.19 ± 4.92	12	0.049
250 ml cranberry + 500 ml water	3.9 ± 3.3	45	4.9×10^{-12}
750 ml cranberry	2.7 ± 2.4	62	2.6×10^{-18}

sion mediated by p-fimbriae is not inhibitable by fructose or other low-molecular carbohydrates (hence mannose-resistent fimbriae).

Antibiotics are the treatment of choice for UTI, but in recent years bacteria have increasingly become antibiotic-resistant. Antibiotics are also administered for long-term prophylaxis of recurrent UTI at a reduced dosage, often at the expense of a disturbed mucosal micro-flora. Other adverse effects of antibiotics explain their poor acceptance in women, who will often ask for more "natural" prophylaxis of recurrent UTI.

Alternative strategies with acceptable evidence are acidification of urine, e. g. by L-methionine, or displacement of uropathogenic bacteria by probiotic lactobacillae at periurethral/perivaginal sites. The latter works well in premenopausal women with a vaginal pH of >5, where vaginal application of *Lactobacillus casei*) reduced UTI by 80%. In postmenopausal women, recurrent UTI can be reduced by local application of estrogens. Another alternative is the vaccination with heat-inactivated uropathogens to prevent recurrent UTI. In a multi-center study of a lyophylisated extract from 18 uropathogenic E. coli strains (OM-89) the incidence of UTI was reduced by 34% [3]. These outcomes are still inferior to antibiotic prophylaxis and have therefore not replaced the standard approach.

Cranberry as UTI prophylactic, historical perspective and modern research on its efficacy and mechanism

The American cranberry (*Vaccinium macrocarpon*) was used by North-American Indians to fight UTI and other infections. Treatment success raised the interest of European physicians and they confirmed its validity. The underlying mechanisms have been investigated in recent years and clinical trials have substantiated the earlier anecdotal observations.

Cranberry's natural distribution is confined to northern America. The closely related European cranberry (*Vaccinium oxycoccus*) yields much smaller berries, which are harvested from the wild in some countries. The lingonberry (*V. vitis-idaea*) and the blueberry (*V. myrtillus*) are other relatives of the cranberry. Lingonberries tend to be confused with cranberries, especially by medical professionals. Lingonberries are also esteemed as a folk-remedy for UTI in central Europe, and they share some constituents with cranberries, but the research evidence for a role in UTI-prophylaxis is limited. Nevertheless, lingonberry-juice was combined with European cranberry juice in one successful study [4].

Proanthocyanidins from cranberries inhibit adhesion of p-fimbriated E.coli

In the past the anti-infective quality of cranberries had been attributed to their content in organic acids [5]. Later, it was discovered that cranberry-juice principally works by inhibiting the adhesion of ubiquitous type 1-fimbriated E. coli, as well as of uropathogenic p-fimbriated strains to uroepithelia [6–8].

Higher-molecular phytochemicals, namely certain types of proanthocyanidins (PAC) from cranberries were identified to selectively possess anti-adhesion activity against p-fimbriated E. coli [7, 8]. PAC are polyphenolic flavanoles; and PAC present in cranberries are oligomers of catechin and epicatechin, which are also classified as condensed tannins due to their denaturing effect on proteins. Catechin- and epicatechin-oligomers have to be biochemically bond as A-type PAC to acquire the anti-adhesive activity. A-type PAC occur abundantly in cranberries, while B-type PAC, present e. g. in green tea or chocolate, are devoid of anti-adhesion activity [9]. Many fruits were also screened in vain for the presence of anti-adhesive PAC.

Cranberry-PAC even abolished the expression of p-fimbriae in E. coli, when added to bacterial culture medium [10]. On the molecular level, a less than 3-hourly incubation of p-fimbriated E. coli with cranberry juice of neutral pH changed the conformation of surface molecules on p-fimbriae, and the adhesive power got lost [11].

Anti-adhesive principle of cranberry-PAC works in humans

Recently, it has been demonstrated by two clinical trials that the anti-adhesive activity of cranberry-ingredients is conserved in human urine following oral ingestion of cranberry-juice [12, 13]. Urine from 10 healthy male volunteers reduced the adhesion of one E. coli strain on silicon rubber after previous cranberry supplementation,

and a further placebo-controlled study in volunteers quantified the anti-adhesive quality of urine after drinking of different amounts of cranberry-juice or placebo by measuring adhesion-rates of E. coli to bladder cells [13]. Drinking cranberry-juice on the previous day caused a dose-dependent drop of adhesion-rates, irrespective of pathogenicity-criteria and/or antibiotic resistance of E. coli. The anti-adhesive quality is first detectable 2 h after cranberry ingestion and lasts up to 12 h later [12].

Randomised clinical trials with cranberries in patients with recurrent UTI

Avorn [14] studied 153 post-menopausal women (mean age 78.5 years) who either drank 300 ml Cranberry-juice daily, or a synthetic placebo-drink with identical taste, colour and sugar-content for 6 months. The combined occurrence of a significant bacteriuria and pyuria in monthly-collected urine samples was significantly reduced in the cranberry group by about 42% over the control group ($p = 0.004$), and there was less need for antibiotic therapy.

Another trial from Finland published earlier this decade received enormous media interest and popularized cranberry-based prophylaxis in Europe [4]. Young women ($n = 150$; mean age 30 y) with previous UTI caused by E. coli were randomly assigned to drink either 50 ml of a so-called cranberry-juice (which turned out to be a mixture of lingonberry juice (*Vaccinium vitis-idaea*) and European cranberry juice (*V. oxycoccus*)) daily for 6 months, or 100 ml of a probiotic *lactobacillus*-drink 5 days per week for 12 months, or to receive no intervention. Patients were followed for 12 months to reach the study end-point of first re-occurrence of symptomatic UTI.

Drinking cranberry-juice reduced the cumulative rate of the first re-occurrence of UTI by 56% versus control-group, but there was no difference between control group and the *lactobacillus*-group. After 6 months the absolute risk for UTI was reduced by 20% in the cranberry-group and the benefit of cranberry-supplementation was still significant after 12 months. The failure of the probiotic *lactobacillus*-drink to promote a periurethral and perianal *lactobacillic* colonisation was retrospectively blamed on underdosage.

Another placebo-controlled trial from Canada in 150 sexually active women (21–72 years old) reaffirmed the prophylactic value of cranberry products for UTI, but furthermore compared capsules of cranberry-extract against cranberry juice, not only for efficacy, but also for costs [15]. The incidence of UTI was lower in both cranberry groups by 20%, and in the cost-efficacy analysis there was a slight advantage for the cranberry-capsules.

The Cochrane-institution has relied on these randomized clinical trials for their recent positive assessment of cranberry-based prophylaxis. The preventive value of this strategy was accepted as evidence-based for women with recurrent UTI [16].

Further questions are addressed by ongoing studies. A well-designed trial has started in the Netherlands (NAPRUTI), testing the non-inferiority of two alternative prophylactic strategies against standard antibiotic prophylaxis with 480 mg Trimethoprim-Sulfamethoxazol daily [17]. Cranberry-capsules will be tested in premenopausal women, a probiotic drink in postmenopausal elderly women, follow-up is planned for 12 months.

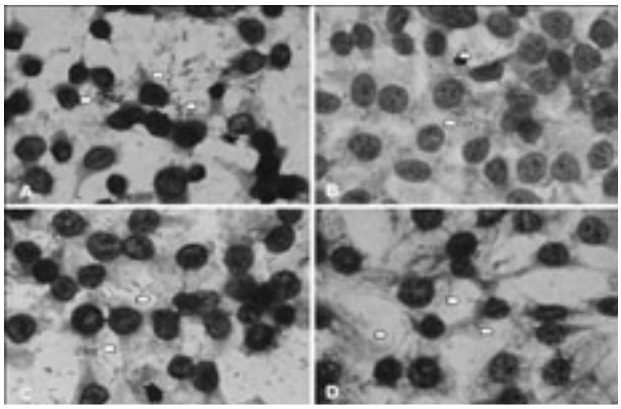

Fig. 1. Adhesion of *E. coli* to uroepithelial cells. **A:** 250 ml placebo + 500 ml water, **B:** 250 ml cranberry + 500 ml water; **C:** 750 ml placebo; **D:** 750 ml cranberry; Bacteria are indicated by arrows [13]

A working prophylaxis of recurrent UTI is most urgently needed in patients with defective anatomy or function of the urinary tract or those with impaired immuno-competence. These patients put a lot of hope into a prophylaxis with cranberries.

Neuropathic bladder-dysfunction following spinal cord injuries predisposes for chronic UTI, often with multiresistent bacteria, because of chronic or intermittent catheterisation. Biofilms, generated along the catheters, are difficult to erase and represent a constant reservoir for bacterial reinfection. Two pilot-studies found a reduction of biofilms by cranberry juice in patients with neuropathic bladder [18], but recent randomized placebo-controlled trials could not confirme a benefit of daily cranberry juice consumption [19].

Renal transplant patients are at increased risk for UTI, especially within the first 3 months post-transplant, when every second patient suffers from UTI. The author himself has observed reduction of symptomatic UTI-episodes in two female transplant-patients after they started drinking cranberry juice. These are currently the only data in transplant patients. Moreover, transplant physicians are often sceptic about herbals, which they fear as a potential source of interactions with immunosuppressive treatments (see below).

Anti-adhesion strategies with Cranberry for other indications

Dealing with bacterial infection just by letting bacteria be swept way from the mucosa is an intelligent strategy with further applications. A possible advantage of the anti-adhesive approach over antibiotics is the absence of selection pressure to acquire resistance. Anti-adhesives have already been utilized in the past, although not rationally and intentionally, with many traditional herbal treatments. The bush *Berberis aristata* in China and the North-American goldenseal (*Hydrastis canadensis*) owe their well-documented efficacy against infection to the

alkaloide berberine. Recent research has shown that berberine reduced adhesion of uropathogenetic *E. coli* to uro-epithelia [20] by abolishing the synthesis of fimbriae and flagellae, which impairs versality and virulence of bacteria.

Presently, rational treatments based on the anti-adhesion mechanism are designed. In veterinary medicine, bacterial decontamination of infected mare's uterus was accomplished by flushing with mannose solution, which eventually improved equine breeding. Bacteria cling to the sugar and get flushed out. Prevention of caries in children by xylitol is another example. Xylitol prevents *Streptococcus mutans* from sticking to teeth, and it has also been investigated whether chewing gum containing xylitol prevents ear infections caused by *Streptococcus pneumoniae* in children, although, not always successfully.

Cranberries offer a solution for a technical problem of microbial contamination of microscope slides in immunoassays by stopping bacterial adhesion. Other fruit juices (grape-, orange-, and apple) tested for that purpose had been inefficacious.

Currently, cranberry-based treatments are being investigated for two common diseases with bacterial pathogenetic contribution: the *Helicobacter pylori* (Hp) associated gastritis and ulceration, and dental caries /periodontal disease.

Cranberry for tooth decay and periodontal disease

Tooth decay and periodontal disease are worldwide plagues caused by pathogenic bacteria resident in the oral cavity, and their metabolic activity. Different bacterial species, notably from the *Streptococcus mutans* group, co-aggregate by adhesion to generate a biofilm on the tooth surface. Within a matrix of salivary proteins these bacteria release enzymes, e. g. glucosyltransferase (GTF) and fructosyltransferase (FTF)), and synthesize fructanes and glucanes that facilitate further bacterial attachment. Metabolic transformation of carbohydrates leads to organic acids that demineralise the teeth. The vicious bacterial biofilm is difficult to attack mechanically by toothbrushes.

Research conducted in the late 1990s at the University of Tel Aviv showed that the high-molecular constituents of cranberry juice reduce and even reverse bacterial co-aggregation in dental biofilm, especially when gram-negative anaerobic bacteria were involved [21]. Cranberry constituents also reduced the enzymatic activity of GTF and FTF within the biofilm and decreased the polysaccharide-synthesis [22]. The adhesion of *Streptococcus sobrinus* to hydroxyapatite could be reduced, partly by a polysaccharide-independent influence. In a further step, high-molecular cranberry-compounds successfully desintegrat the dental plaques by separation of *Streptococcus sobrinus* from the biofilm. Preincubation of S*treptococci* with cranberry extracts reduced the biofilm generation. These promising „in vitro" results performed with artificial biofilm have been followed by an affirmative clinical trial. Two groups each with 30 volunteers were randomized to use either a daily cranberry

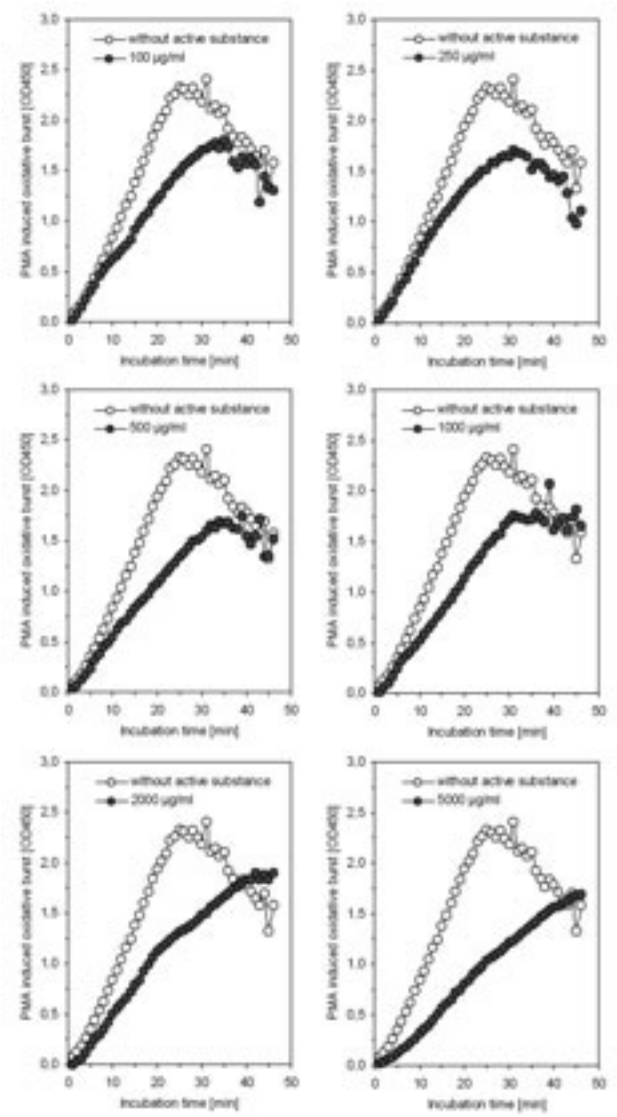

Fig. 2. PMA-induced oxidative burst of differentiated HL60-cell after incubation with different concentrations of cranberry juice (Fa. Töpfer) (Dartsch PC. Wissenschaftliches Gutachten im Auftrag der Fa. Töpfer GmbH; 2006)

mouth-wash or a placebo mouth-wash for 6 weeks, resulting in a significant reduction of salivary bacteria and notably of *Streptococcus mutans* in the cranberry-group [22].

Cranberry macromolecules may also improve periodontal disease. They were shown to halt bacterial production of pro-inflammatory cytokines and proteolytic enzymes after induction by lipopolysaccharide (LPS) [23]. The reduction in biofilm-formation and acidogenicity by *Streptococcus mutans* could specifically be attributed to cranberry-PAC, and mainly to type A-oligomers of epicatechin, which corresponds well to the importance of these phytochemicals in cranberry-based UTI-prophylaxis.

Helicobacter pylori infection

Gastritis and peptic ulcer disease are strongly associated with the mucosal presence of the bacterium *Helicobacter*

pylori (Hp). The discovery of bacterial etiology had changed the therapeutic concept, and Hp-positive gastritis or duodenal ulcers are now treated with combinations of antibiotics to eradicate Hp-colonisation.

Not surprisingly, about two decades since this change in therapeutic policy, resistance of Hp towards antibiotics is rising, and this has stimulated the search for novel treatments. A promising approach aims at the adhesion processes that are necessary to establish the Hp-infection.

High-molecular fractions of cranberries inhibit the adhesion of Hp to gastric mucus and mucosal cells "in vitro" [24]. This inhibition of adhesion by cranberry extracts also works for Hp-isolates with antibiotic resistance, e. g. against metronidazole, and the efficacy of clarithromycin against Hp was increased by co-administered cranberry juice, as well as by other berry juices. This suggests that cranberries could be an adjuvant for eradication of Hp, especially in the circumstances of antibiotic resistance.

A clinical trial performed in an area of endemic Hp-infection in China supports the benefit of cranberries in this indication. Half of the 189 patients tested positive for Hp-infection by 13 C urease breath-test drank 250 ml cranberry juice daily for 90 days, while the others received a placebo-drink. After 35, and 90 days, respectively, fewer patients were tested positive for Hp in the cranberry-group.

Quality criteria of cranberry products

Once the anti-adhesive capacity of cranberry-PAC had been discovered, the PAC-concentration necessary in cranberry products to obtain this desired health effect was asked about. This question cannot be answered today. Clinical trials have used different juices or extracts, which had not been standardized for their richness in PAC.

A dose-effect relationship of cranberry juice has never been established. However, the results of the trial by Di Martino et al ([13] see above), suggest that the strength of the anti-adhesive effect in human urine depends on the ingested amount of cranberry juice.

Despite the documented role of PAC for anti-adhesion, it would probably be premature to exclusively focus on these cranberry ingredients. Many other cranberry constituents may in one or the other way contribute to the observed effects against bacterial infection. A side-glance at another research field of cranberry phytochemicals tells us that the anti-proliferative activity on several tumor cell lines is the synergistic effect of many compounds in total cranberry extracts, rather than of single components, as had been proposed before [25].

Another way to assure a high-quality cranberry juice is by measuring its anti-oxidative power [26]. Cranberries rank among those fruits with the highest content in anti-oxidatives, and can powerfully protect from LDL-cholesterol oxidation. The anti-oxidative capacity of cranberries is linked to their content in catechins and PAC [27], and richness in these therapeutically desired phytochemicals can indirectly be quantified by measuring the anti-oxidative status.

Safety of cranberry products

There are few anecdotal reports about adverse effects, some of them can most likely be explained by an unreasonably high intake of cranberry juice. Cranberry juice drinking was supposed to have caused deranged coagulation parameters and bleeding in patients on chronic warfarin treatment. It was hypothesized that cranberry ingredients had increased warfarin's bioavailability by interactions with the cytochrome P 450 enzymes. A randomized trial could not confirm changes in prothrombin time of warfarin-treated males by consumption of 250 ml commercial cranberry juice daily [28]. Given today's popularity of cranberry-juice drinking, many more incidents and reports of bleedings should be expected if the attributable risk was really significant.

Another concern is the trough level adjusted immunosuppressive treatment of transplant patients, which is evidently vulnerable by herbal drugs that modify cytochrome P 450 enzymes and drug-transporting proteins. Despite the absence of reported incidents, a clinical trial recently addressed the impact of cranberry juice on cyclosporin pharmacokinetics in volunteers and found no clinical interaction [29]. Finally, the role cranberry juice may play in promoting the formation of kidney stones is being discussed, but the results of studies are inconclusive. In volunteers, and known calcium-oxalate stone formers, cranberry juice had mixed effects on urinary-stone-forming propensity. A randomized cross-over trial from South-Africa even found anti-lithogenic properties of cranberry juice.

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