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Cranberry components for the therapy of infectious disease

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Summary of the *in vitro* data support a beneficial effect of cranberry or its proanthocyanin constituents by blocking adhesion to and biofilm formation on target tissues of pathogens. *In vivo* data partially support these beneficial effects. Consumption of various cranberry products benefited young and elderly females in preventing urinary tract infections, and in conjunction with antibiotic treatment in eradicating *Helicobacter pylori* infections in women. Mouthwash supplemented with an isolated cranberry derivative reduced significantly the caryogenic mutans streptococci. None of the mice infected intranasal with lethal dose of influenza virus and treated with cranberry fraction died after two weeks. Further studies should focus on the active cranberry component as supplement for food and other products especially where whole juice or powder cannot be used.

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Introduction

Since the discovery four decades ago that adhesion of pathogens to soft and hard tissues is essential for initiating infection, research has been focused toward effective anti-adhesion therapy for treating or preventing infectious diseases [1,2]. Unlike bactericidal agents, the use of anti-adhesion agents are expected to attenuate the selection of resistant strains which are diluted out by the sensitive strains as viability of both type of strains is not affected. Dietary anti-adhesion agents has been the focus of intensive research because such natural agents are likely to be non-toxic. Furthermore, the identified active components can be used as food supplement negating the necessity to adhere to a particular diet.

Perhaps most important advantage of searching dietary agents is that approval of clinical trials is easier to obtain, as toxicity is not an issue. In this respect, cranberry juice and isolated fractions/constituents have been studied the most with respect to both *in vitro* and *in vivo* experiments including human trials. In this review we will summarize the accumulating *in vivo* and supporting *in vitro* studies suggesting beneficiary effects of cranberries or its constituents for treating or preventing microbial diseases. In particular cranberry effects on urinary tract infections (UTI) caused by *Escherichiae coli*, infectious gastritis or peptic ulcer diseases induced by *Helicobacter pylori*, entero and influenza viral infections and oral health will be discussed.

Urinary tract infections

Native Americans recognized the beneficiary effect of ripe cranberry fruit in bladder and kidney disorders among other diseases [3]. Since the introduction of cranberry juice cocktail in 1930, cranberry juice became widely recommended for the treatment of UTI. However, presence of bactericidal agents in cranberry or acidification of urine after cranberry consumption could not be found in spite of clinical beneficiary effect [4].

During the last three decades *in vitro* studies has confirmed that cranberry constituents inhibit adhesion of P-fimbriated uropathogenic *E. coli* to their cognate gal–gal receptor present on epithelial cells as well as on other cells. P-fimbrial receptor is also present on erythrocytes, which undergo hemagglutination upon mixing with P-fimbriated *E. coli*. Inhibition of hemagglutination has become the test of choice in assays for anti-adhesion activity of cranberry constituents.

Box 1 summaries the *in vitro* and *ex/in vivo* studies showing that cranberry or high molecular weight non-dialyzable material (NDM) or proanthocyanins (PAC) constituents, inhibit selectively the adhesion of P-fimbriated uropathogenic *E. coli*, the most common cause of UTI. Table 1 summarizes the double-blind clinical trials that met inclusion criteria (randomized to control or treatment) on the effect of cranberry on UTI based on Cochrane Database metanalysis of studies up to 2008 [5••]. Juice formulation was used in six studies, tablet formulation in 3 studies and both formulations were used in one study.

Box 1 *In vitro* **and** *ex vivo* **studies showing anti adhesion activity of cranberry juice and cranberry constituents against uropathogenic** *E. coli*

- Cranberry juice but not other juices inhibits hemagglutination and uroepithelial adhesion of P-fimbriated uropathogenic *E. coli* [29,30].
- A-type proanthocyanidins composed of epicatechin oligomers, with at least one A-type linkage (double bonds between two epicathechin: 4 > 8 and 2 > O > 7 interflavan bonds) and a high molecular weight nondialysable material (also known as NDM) that contains polyphenols, probably of A-type epicathechin polymers, all of which obtained from cranberries or cranberry juice inhibit adhesion and hemagglutination of uropathogenic *E. coli* but not diarrheal *E. coli* [8,29,31]. B-type proanthocyanidins with one B-type linkage (one bond between epicathechin units: 4 > 8 interflavan bond) obtained from other plants was without effect.
- Urine from individuals or rodents consuming cranberry exhibit anti adhesion activity of uropathogenic *E. coli* [31,32•].

Jepson *et al.* [5••] concluded that studies support the potential use of cranberry products in the prophylaxis of recurrent UTIs in young and middle-aged women. However, the efficacy of cranberry in other groups (i.e. elderly, pediatric patients, patients with neurogenic bladder, or chronic indwelling urinary catheters) is questionable. The high withdrawal rates (up to 55%) in these studies, suggest that these formulations may not be acceptable over prolonged use. More recently it was found that consumption of 27% cranberry juice cocktail for 6 months (240 ml twice per day of low calorie juice) by young college females (mean age 21 ± 3) was ineffective in preventing UTI as compared to placebo [6]. Lack of 'adequately powered placebo-controlled trials' was proposed by the authors to explain the unexpected failure of cranberry treatment compared to studies in Cochrane review. However, there could be a number of other explanations, one of which is that in previous studies cranberry juice cocktail was sweetened with fructose while in the young females study, low calorie, sucralose sweetened, juice was used. It was shown that the fructose inhibits the type-1 fimbrial adhesin expressed by all P-fimbrilated uropathogenic *E. coli* emphasizing the notion that the beneficiary effect of cranberry juice cocktail may be due to two inhibitors (fructose and PAC) each specific for a distinct adhesin [7,8]. Another explanation may be related to the study population that is young females who experience 2–3 times a week sexual intercourse [6]. It was reported that urinary *E. coli* counts increased transiently approximately ten-fold after sexual course in nearly half of the volunteers [9]. Sexual activities decline with increasing age [10]. Thus, it is possible that the young females requires either fructose sweetened juice or higher dose of low calorie juice to cope with increase in vaginal *E. coli* counts. However, consumption of higher dose of cranberry juice over a long period 'may not be acceptable' as suggested by low compliance [5••,4,11•]. To overcome this, there is a need to isolate most active anti-adhesion cranberry constituents and use them as supplements to other juices for the control of UTI. Such approach may now be feasible with the isolation of highly active fractions from cranberries (Box 1).

Cranberry components remain the only nutritional therapy clearly demonstrated to be effective in preventing an infectious disease [12], and it is approved by French Agency for Food Safety (AFSSA), to be marketed as urinary health promoters.

Gastric, duodenal and peptic ulcers

H. pylori a gram negative bacterium, is associated with gastrointestinal diseases including gastric, duodenal and peptic ulcers, as well as gastric cancer, and gastric lymphoma [13]. It is one of the most common chronic bacterial infectious diseases in man. More than half of the world population is infected early in life (almost always before the age of 10 years), and in the absence of antibiotic therapy, it generally persists for life. *In vitro* studies indicated that the high molecular weight obtained from cranberry juice inhibits the siallylactose-specific (S-fimbriae) adhesion of *H. pylori* strains to immobilized human mucus, erythrocytes and cultured gastric epithelial cells [14,15,16]. The adhesion of two-thirds of 83 *H. pylori* clinical isolates to gastric cell line was inhibited by 0.2 mg/mL of cranberry

Table 1

Double-blind clinical trial on the effect of cranberry on UTI in females

Study group	Range or mean age	Number of:		Type of UTI	Beneficiary effect on UTI
		Studies	Patients		
Young	21	1	319	Symptomatic	No
Adults	31–42	3	318	Symptomatic	Yes
Eldery	81–82	2	405	Symptomatic	No
	78.5	1	192	Pyuria	Yes
Patients with catheterization					
Children	9–18	2	55	Symptomatic	No
Adults	NA	2	69	Symptomatic	No

Data based on 10 studies reviewed by Jepson *et al.* [5] and based Cochrane review.

Table 2

Anti-cariogenic and anti-periopathogenic bacteria and anti-inflammation processes of cranberry components

Biological activity				
Cranberry components	Anti-adhesion Anti-coaggregation	Anti-enzymatic	Anti-biofilm formation	Anti-acidants production
A. Anti-cariogenic bacteria				
NDM	+	+	+	+
PAC, flavonols	NR	+	+	+
B. Anti-periopathogenic bacteria				
NDM	+	+	+	IRR
C. Anti-inflammatory processes				
NDM	IRR	+	IRR	IRR

Data based on studies reviewed by Bodet *et al.* [33••], and [34–37,28•].
NR, not reported; IRR, irrelevant.

NDM [17]. There was no relationship between the anti-adhesion effect of the cranberry and bacterial resistance to metronidazole. These data suggest that a combination of antibiotics and a cranberry preparation may improve *H. pylori* eradication. This additive effect was assessed in a recent double-blind clinical study in which one group of 170 patients with elevated 13C-urea breath test (e.g. infected with *H. pylori*) were treated with antibiotics for 1 week and randomly allocated to receive 250 mL of either cranberry juice or placebo [18]. Additional control group consisted of 712 patients who were treated with antibiotics alone. Analysis by gender revealed that for female subjects, the eradication rate was significantly higher in the cranberry-antibiotic arm reaching 95% than in the placebo-antibiotic arm and also significantly higher than in the antibiotic group (80% and 83%, respectively). These results suggest that the addition of cranberry to triple therapy improves the rate of *H. pylori* eradication in females. Double-blind placebo-controlled clinical trial employing patients with elevated 13C-urea breath test, supported this conclusion. In this study the patients were randomized in two groups one of which was asked to drink cranberry only and the other placebo juice only of 500 mL daily for 90 days [19].

Although the overall rate of eradication of *H. pylori* was low in the range of 5–17%, the eradication rate in the cranberry group (14.3%) was significantly higher as compared to the placebo group (5.2%).

Experimental infection in mice treated with cranberry revealed that although the microorganisms were not eradicated there was a marked reduction in the total helicobacter mass after consumption of cranberry alone [20]. It appears that cranberry consumption alone may reduce the total helicobacter mass rather than eradication of all bacteria. Such outcome may especially benefit pregnant women where antibiotic treatment is not recommended. Furthermore, cranberry juice may become a treatment of choice in view of the recent reports showing a strong association between complete eradication of helicobacter colonization and emergence of esophagus cancer [21]. More clinical trials in different populations are needed to confirm the effect of cranberry juice with or without antibiotic treatment for the control of *H. pylori* bacterial mass.

Viral diseases

Cranberry and its PAC and NDM fractions were found to inhibit the infectivity of a number of viruses in target cell lines or the interaction of the influenza virus with its receptor on erythrocytes (e.g. hemagglutination). Significantly, cranberry juice inhibited infectivity of enteroviruses [22,23], PAC inhibited surrogate enteroviruses [24,25] and NDM inhibited influenza virus in cell cultures [26].

Although these studies suggest that consumption of cranberry juice or its constituents may benefit infections caused by the above viruses, there is still no published *in vivo* or clinical data to support this conclusion. In preliminary mice study (Rones *et al.*, in preparation) it was found that intranasal infection of mice with viral suspension supplemented with 0.2 mg/ml NDM resulted in a significant protection of the mice against morbidity and mortality caused by influenza virus infection. In addition there was a reduction of viral titers in the lungs, and the lungs histopathology showed almost no damage to the alveoli epithelium compared to sloughing, necrosis and polymorphonuclear neutrophilic granulocyte infiltration seen in the viral group. This provides promising perspectives for the development of novel anti-influenza adjunctive therapies.

Oral health

There are numerous *in vitro* studies showing that cranberry components such as PAC or NDM inhibit adhesion of oral bacteria including adhesion to teeth surfaces and to epithelial cells as well as of bacteria to each other (e.g. intergenera/species coaggregation) (Table 2). NDM and PAC were found to inhibit key bacterial enzymes involved in adhesion and in biofilm formation on teeth surfaces such as glucosyl and fructosyl transferases as well as tissue damaging bacterial enzymes such as gingipain of

Figure 1

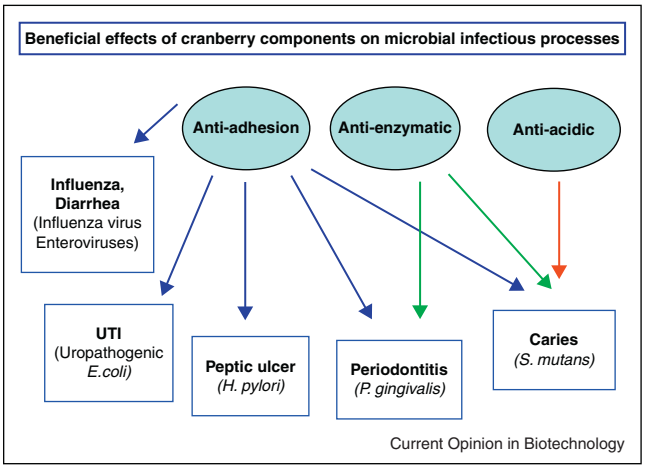

Diagram showing processes affected by cranberry components leading to beneficiary effects for preventing/treating various microbial diseases. Only infectious diseases for which there are at least one human trial and/or experimental infection using cranberry components are included. More details on such *in vivo* experiments and supporting *in vitro* studies are reviewed in the text.

the periopathogenic *P. gingivalis* bacteria. In addition, the cranberry components inhibit acid production by cariogenic bacteria. Of special interest are the observations that NDM inhibits host enzymes that participate in periodontal diseases such as MMP-3 and MMP-9 and elastase. Induction of proinflammatory cytokines such as IL-1beta, TNF-alpha, IL-6, IL-8 and RANTES, are also affected. In spite of these *in vitro* studies, there are only two *in vivo* studies using cranberry components. In a clinical trial the effect of mouthwash supplemented with NDM on oral hygiene of healthy volunteers was assessed. Following 6 weeks of daily usage, the salivary mutans streptococci count as well as the total bacterial count were reduced significantly compared to the placebo control group, although no clinical changes in the plaque and gingival indices were observed [27]. Recently, Koo *et al.* [28•] showed in animal study that topical application (twice daily) of PAC onto rat teeth surfaces decreased incidence and severity of *S. mutans* induced smooth-surface as well as sulcal surface caries.

Concluding remarks

There are a number of conclusions from the clinical trials and *in vitro* studies to be implemented for improving oral health or treating/preventing certain microbial diseases such as peptic ulcer, UTI, and infections caused by enteroviruses and influenza virus (Figure 1). Perhaps most important is the realization that the anti-infectious goal can be achieved by employing cranberry fractions or constituents as food supplements. Tablets or powdered whole fruit is not expected to be beneficial as food supplement because the active ingredients are likely to be less than 3% of the dry solid. It has been stressed that prevention of UTI for prolonged period may not be tolerated by a large segment of consumers. Same argument may be used for prevention of *H. pylori* infections or enteroviral infections. In oral health, where generally sugars or acids are harmful, only isolated components can be considered for health maintenance. In upper respiratory viral infections cranberry products as inhalers may be considered. Future clinical studies, therefore, should focus on using cranberry constituents that best fit the maintenance of health balance of the infectious diseases discussed in this review and, at the same time, are economically affordable.

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