

## THE SCIENCE BEHIND CRANBERRY FOR URINARY TRACT HEALTH

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### REVIEW OF CRANBERRY FOR PREVENTION OF URINARY TRACT INFECTIONS

Cranberries have been used for centuries for the prevention of urinary tract infections (UTIs) in people. Daily quantities of cranberry juice or a concentrated cranberry extract have been shown to be effective in decreasing or eliminating the recurrence of UTIs in women prone to recurrent UTIs.<sup>1,2</sup> The cranberry literature has been reviewed by the Cochrane Collaboration, which found that there is good evidence for UTI prevention following regular cranberry consumption,<sup>3</sup> but not enough to recommend cranberry alone for treatment of UTIs.<sup>4</sup> Initial theories proposed that cranberries worked by acidifying the urine; however, with normal cranberry juice consumption the urine pH may decrease, but not sufficiently nor consistently to be bactericidal.<sup>1,5,6</sup> Important virulence factors in the pathogenesis of UTIs include bacterial adhesins (P fimbriae and type 1 fimbriae) that adhere to carbohydrate receptors on the surface of uroepithelial cells.<sup>7</sup> Nearly all uropathogenic strains of *Escherichia coli* (*E coli*) can express type 1 fimbriae that bind to mannose-like receptors.<sup>8</sup> P-fimbriated *E coli* adhere to oligosaccharide receptor sequences,<sup>9</sup> and have been associated with both cystitis and pyelonephritis.<sup>10</sup> Research has shown that the active components of the cranberry are a group of compounds called proanthocyanidins (PACs) or condensed tannins, and that their mechanism of action is inhibiting the adhesion of P-fimbriated *E coli* to the uroepithelium.<sup>11</sup> Bacterial adhesion to cells is the initial step in the infection process.<sup>12</sup> If the initial adhesion step is inhibited, the bacteria are not able to multiply and colonize, essentially preventing infection. The advantage of this mechanism is that it should not promote antibiotic resistance nor lead to significant selection pressure favoring survival of antibiotic-resistant bacterial strains, because the bacteria are not killed.<sup>13</sup> This type of preventative strategy could become more important as antibiotic resistance rates continue to increase because of over-use of antibiotics.<sup>14</sup> Thus, utilization of cranberry to prevent certain bacterial infections could potentially aid in reducing the pace of antibiotic resistance development.

PACs, the compounds associated with the bacterial anti-adhesion activity in cranberry, are defense compounds produced in response to environmental stress and microbial infection.<sup>15,16</sup> Their astringency protects the young fruit from animal and insect predation.<sup>17</sup> They are polyphenols<sup>18</sup> linked through either single bonds (B-type), as in grape and chocolate PACs,<sup>19</sup> or less commonly through double bonds (A-type), as in cranberry.<sup>20,21</sup> Cranberry PACs are mainly

epicatechin units with at least one A-type linkage. Research suggests that the bacterial anti-adhesion activity may be due to the A-type linkages in cranberry PACs, because the B-linked PACs found in other common foods such as grape and chocolate do not possess this anti-adhesion activity, nor do these foods elicit this activity in the urine.<sup>22</sup>

The bacterial anti-adhesion mechanism of cranberry is being studied. The proteinaceous fimbrial tips on the bacteria bind to mucosal surfaces on the uroepithelium as a specific receptor-ligand association<sup>23</sup> favored by hydrophobic interactions.<sup>24</sup> Cranberry, including PACs and/or their metabolites, may act as receptor analogs and competitively inhibit adhesion to cells by binding to the bacterial fimbrial tips. Other modifications to the bacteria may be occurring that influence adhesion potential. For example, bacterial cell surface properties may be altered,<sup>25</sup> conformational changes in the surface macromolecules of the *E coli* may occur,<sup>26</sup> cranberry may down regulate flagellar basal body rods and motor proteins to decrease P-fimbriae,<sup>27</sup> and fimbrial expression may be reduced at the genetic level.<sup>26,28</sup> Changes in bacterial morphology from rods to spheres have occurred following incubation in cranberry juice,<sup>26</sup> and from rods to elongated rods.<sup>28</sup> Further research is necessary to determine how these changes may affect the adhesion process.

Biological assays are utilized to detect bacterial anti-adhesion activity of cranberry and isolated cranberry PACs, including mannose-resistant hemagglutination (MRHA) (for *E coli* expressing papG, Dr/Afa, and S adhesins),<sup>20,21,29,30,31</sup> Gal-Gal receptor bead agglutination,<sup>11,31</sup> bladder epithelial cell adherence,<sup>29-33</sup> and microplate-turbidity.<sup>34</sup> Utilizing a bioassay to detect *in vitro* anti-adhesion activity of whole cranberry products and isolated PACs is useful for determining product integrity; however, it does not assess *in vivo* activity of the post-ingested cranberry metabolites, which may not be proanthocyanidin in nature. Urinary bacterial anti-adhesion activity may be a more biologically relevant marker for cranberry ingestion as well as assessing effectiveness for prevention of UTI. The MRHA assay has been utilized for detecting anti-adhesion activity both *in vitro* and *ex vivo* in urine following ingestion of cranberry products.<sup>20,22</sup>

Women given single doses of cranberry in the form of cranberry juice produced urine that could inhibit the activity of P-fimbriated *E coli* *in vitro* within 4 to 6 hours of oral administration.<sup>22</sup> This effect lasted at least 8 hours. Mice given cranberry juice or cranberry PACs in their drinking water for 30 days had inhibition of P-fimbriated *E coli* in their urine within 5 days of administration.<sup>35</sup> This result showed a dose-dependent inhibition of P-fimbriated *E coli*. Cranberry has also been shown to have an effect on biofilm formation and recurrent UTIs and this may be useful in catheterized animals. A biofilm is an aggregate of bacteria adhering to each other and/or to a surface and are frequently within a self-produced matrix of extracellular material consisting of DNA, proteins and polysaccharides. This

matrix is protective to the cells and may aid in protecting bacteria from antibiotics or it may aid in the dispersal of bacteria to new sites. Cranberry PACs prevented nonspecific adhesion of both *E coli* and *Enterococcus faecalis* to two common biomaterials used in the manufacturing of catheters.<sup>36</sup> Cranberry juice administered for one week showed a reduction in biofilm formation in spinal cord patients as compared with water.<sup>37</sup> The PACs in cranberry have also been linked to prevention of *Helicobacter pylori* adhesion in the stomach<sup>38</sup> and prevention of biofilms in the oral cavity.<sup>39</sup>

## REVIEW OF CANINE UTI

Bacterial UTIs are common in dogs (2%–14%), but less so in cats (1%–2%) less than 10 years of age.<sup>40,41</sup> Similar to humans, female dogs have more UTIs than males. The predominant bacteria isolated in canine UTIs is *E coli* accounting for up to 37% to 45% of UTIs.<sup>42</sup> Dogs with a UTI caused by *E coli* or *Proteus* usually had the same organism in their intestinal tracts and prepuce or vagina.<sup>42</sup>

Due to a strong human–animal bond, the transmissibility of *E coli* infections from dogs to people (or vice versa) has been a public health concern. One study showed that almost 10% of the fecal *E coli* colonies isolated from healthy household dogs were the same as those present in their healthy owners. It was suggested that transmission could have occurred in either direction.<sup>43</sup> Highly similar and in some cases identical phenotypic and genotypic characteristics of canine and human extraintestinal pathogenic *E coli* were observed for the allele which codes for the P fimbrial adhesin.<sup>44</sup> Low et al. also isolated four strains of canine *E coli* from dogs with UTIs and six strains of human *E coli* from people with UTIs and found closely related or identical strains.<sup>45</sup>

The development of a UTI requires a change in the host defense system and the bacterial interrelationship. Disease, anatomy, drugs and/or catheters may cause a change in the host's defense mechanisms allowing bacterial invasion. Dogs with diabetes mellitus or hyperadrenocorticism and/or treated chronically with steroids have more bacterial UTIs than normal dogs and have a higher percentage of *E coli* UTIs.<sup>46,47</sup> The use of indwelling urinary catheters in veterinary medicine has also been responsible for bacterial UTIs in dogs. Hospitalized dogs with indwelling catheters were 19% to 42% more likely to have a UTI than those not catheterized. There was an increase in infections for each year in age, for each day catheterized and for those on antimicrobials. *Enterobacter* spp and *Staphylococcus* spp were most frequently isolated from the catheterized dogs.<sup>48,49</sup> In catheter-induced *E coli* UTIs, the virulence of the *E coli* and the type of catheter material may play a role in the biofilm development. Some silicone and silicone-latex catheters actually select for and promote a biofilm formation of the most virulent group of *E coli* strains.<sup>50</sup>

The use of antibiotics in the treatment of UTIs requires that the appropriate antibiotic be chosen (preferably by

bacterial culture and antimicrobial sensitivity), and that the duration of the therapy be adequate. Antibiotics and antibiotic therapy have their own inherent problems and may cause gastrointestinal upset, which may lead to decreased drug administration, decreased pet acceptance, or possibly decreased absorption leading to inadequate blood or urine levels. Any of these factors may decrease the elimination of bacteria following the antibiotic therapy and are likely to contribute to bacterial resistance to antibiotics. Because cranberry appears to work well in the prevention, but may not in the treatment of UTIs, antibiotics may be indicated.<sup>3,4</sup> The co-administration of cranberry with two  $\beta$ -lactam antibiotics did not alter the pharmacokinetics of the antibiotics in women.<sup>51</sup>

Relapsing UTIs or recurring UTIs are those that return after the antibiotic therapy has been completed or prematurely discontinued. A relapse may be due to an inadequate duration of therapy or due to the inability of the antibiotic to reach the location of the bacteria such as in a prostatic cyst or in a biofilm. A relapse may occur soon after the antibacterial regimen is stopped, or it may be delayed in time, giving the appearance of a new infection. A bacteria's antimicrobial sensitivity may change making it difficult to determine whether this is a new infection or a relapse.<sup>52</sup>

Antibiotic resistance has become a matter of concern, for both human and veterinary health. Changes in antimicrobial resistance patterns were studied in canine uropathogens collected at a veterinary teaching hospital from January 2002 to June 2007. The rate of bacterial resistance was greatest in dogs with recurrent *E coli* infections.<sup>53</sup> A case report from the University of Georgia identified *E coli* resistant to twelve antibiotics isolated from two dogs in a span of two weeks.<sup>54</sup> Human strains of *E coli* from women with urinary tract infections and pyelonephritis had more drug resistance than the enteric *E. coli* of healthy dogs. The only resistance phenotype that was more common among canine isolates than human isolates was resistance to sulfisoxazole. The results show that antibiotic resistant strains of *E coli* in people were unlikely to have originated from dogs and that possibly dogs could acquire resistant strains from people.<sup>55</sup> The use of cranberry to prevent infections in both canine and human populations could offer a potential alternative UTI prophylaxis and reduce the likelihood of increasing antibiotic resistance.

## USE OF CRANBERRY FOR PREVENTION OF CANINE UTI

There are currently several veterinary products on the market using cranberry material or extracts marketed for the purpose of managing urinary tract health in dogs. A key aspect of a product's activity is the presence of bioactive PACs, as well as the maintenance of the bioactivity of the PACs in the product. Nutramax Laboratories, Inc. has developed Cranandin, a concentrated cranberry product in which the bioactivity of the PACs (16 mg/tablet) is maintained. Other veterinary products were tested and results showed that

while varying amounts of PACs were present (no products were labeled for PACs), all the products tested had very little to no activity. Cranadin has been evaluated in an *ex-vivo* model of urinary bacterial anti-adhesion using the MRHA assay.<sup>30</sup> The dose in dogs was determined to be different from people. Dogs were dosed with one tablet daily of Cranadin (approximately 1 mg PAC/kg body weight). Cranadin showed activity (inhibition of P-fimbriated *E coli* adhesion) in dog urine within 3 hours of the first dose. By Day 7, the average anti-adhesion activity in the urine was 78% and this continued throughout the 21-day dosing period. Cranadin's activity persisted for at least 3 days following the discontinuation of Cranadin. Cranadin will be further evaluated in future studies.

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