Editorial

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Did cranberry fail to show its ability to protect against recurrent urinary tract infections?

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On 27 October 2016, one of the most prestigious medical journals in the world, JAMA, published a negative double-blind and placebo controlled clinical study conducted by researchers from Yale (USA) in which a highly standardized, proanthocyanidin-A (PAC-A)-containing cranberry extract was used [1]. According to the conclusion of the trial: 'Among older women residing in nursing homes, administration of cranberry capsules vs placebo resulted in no significant difference in presence of bacteriuria plus pyuria over 1 year'. An editorial by LE Nicolle in the same issue of *JAMA* flatly condemns the use of cranberry PACs to prevent urinary tract infections (UTIs) and calls on healthcare providers to stop using cranberry and switch back to antibiotics [2].

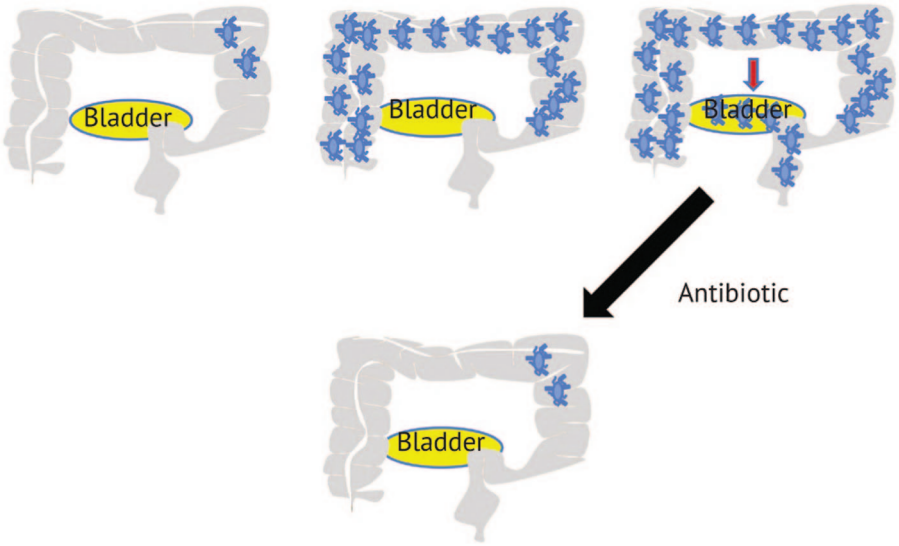
Are the results totally correct? Are the suggestions proposed (to stop cranberry use) appropriate? After reading the report of this clinical trial in *JAMA*, one can immediately understand why, in all likelihood, the study produced negative results: instead of recruiting women who had suffered from recurrent infection, 95% of the women included were healthy without any mention of prior UTI. From a medical perspective, the difference between healthy women and those with recurrent UTI is huge. Most clinical papers on the use of cranberry have found it has a role in preventing recurrent UTI [3]. Obviously, in order to be efficacious, cranberry must be administered when urine culture is negative and to patients in whom a new positive urine is expected within the next 4–8 weeks. This phenomenon is called recurrence and is different from relapse where infection by residual bacteria not eliminated by antibiotic therapy flares up again. In most cases, recurrence seems to be caused by bacterial transmigration, which occurs, mainly in females, due to the anatomical proximity of the intestine to the bladder, allowing bacteria to cross the septum separating the two organs [4]. PAC-A, by interacting directly with P-type fimbriae present in uropathogenic strains of *Escherichia coli* (as in other flagellated strains) prevents the fimbriae from binding to glycoprotein receptors on the bladder epithelium.

The efficacy of cranberry in preventing recurrence raises some points. Uropathogenic *E. coli* and many other flagellated strains typically involved in recurrent cystitis, are positive for at least two types of adhesins localized at the level of cilia and flagella: type-1 pili and P-type structures.

The latter, as mentioned above, interact directly with glycoprotein located on the uroepithelium which facilitates germ proliferation in the bladder. PAC-A also interacts with P-type structures to mechanically prevent binding to the uroepithelial receptor. Type-1 pilus, whose presence alone does not determine uropathogenic status, is a mannose-sensitive protein structure which allows the bacterium to touch the intestinal mucosal membrane, and in some circumstances, pass through it. The following question then arises: PAC-A in cranberry protect against recurrent cystitis but are polyphenolic structures and consequently have poor oral

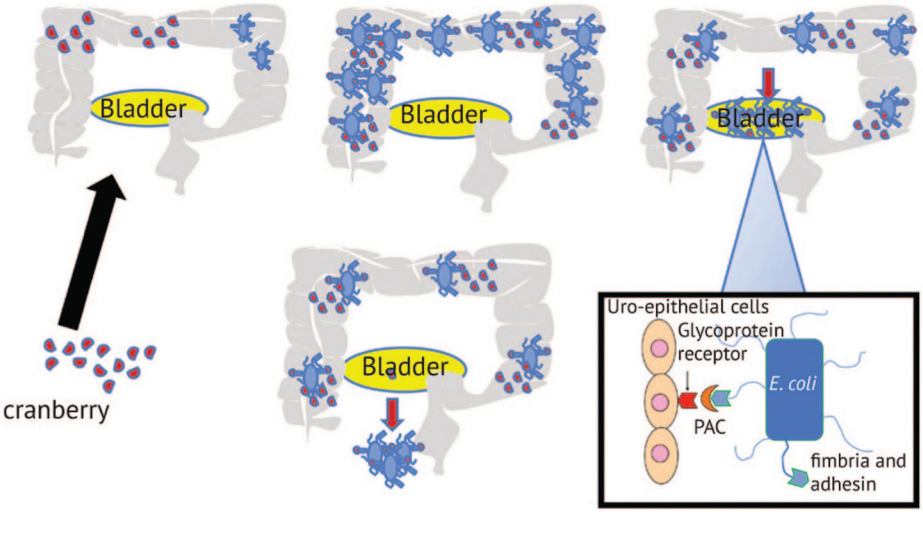
bioavailability, so how do they reduce the proliferation of bacteria in the bladder? PAC-A, like most other polyphenolic structures obtained by extraction, have poor bioavailability and mostly remain unabsorbed in the intestine [5]. However, recurrent cystitis depends on the intestine acting as a culture medium tank for germs. Recurrence is usually found in young women associated with their menstrual cycle, in elderly women and/or in subjects with poor intestinal motility.

The most likely hypothesis is that the bacteria themselves transfer PAC-A which attach themselves to the P-type structures when still in the intestine. However, the bacteria do not use the protein to bind to the receptors and the intestinal epithelium structures in order to proliferate and transmigrate but use type-1 pili which, being PAC insensitive, are available when the bacteria are in the intestine. Once they have transmigrated into the bladder, the bacteria must attach themselves to a structure in order to proliferate as they cannot simply float in the urine which typically occupies the bladder trigone. The problem is that while receptors on the uroepithelium are free, P-type fimbriae are not as they have already been occupied by PAC while the bacteria were still in the intestine. Consequently, the bacteria are expelled during urination as they cannot attach to the uroepithelium. The different roles of antibiotics and cranberry in the treatment and prevention of recurrent cystitis are shown in Figs. 1 and 2.



Uropathogenic strains (blue) are present in the gut of the "healthy" subject; proliferate and transmigrate by type-1 pili to bladder determining colonization and then possibly infection by type-P fimbriae. Antibiotic treatment erases infection but some clones of pathogens could survive in the gut ready to determine a new "recurrent" episode.

Figure 1 - The role of antibiotic therapy in the treatment of recurrent cystitis



While uropathogenic strains (blue) are present in the gut of the "healthy" subject, cranberry PAC-A (red) are given and reach the gut where bind type-P fimbriae without affecting strains proliferation and/or transmigration to bladder by type-1 pili. Colonization and possibly infection is then blocked by PAC-A halting interaction between P-fimbriae and specific receptor on uroepithelial cells. Not colonizing strains are eliminated by the urine.

Figure 2 - The role of cranberry in preventing recurrent cystitis. PAC proanthocyanidin

In conclusion, the negative results described in the JAMA paper could be the results of a mistake in enrolment. By recruiting subjects without recurrent UTI, the Authors have failed to demonstrate the true role played by cranberry PAC-A in limiting adhesion to bladder cells by bacteria migrating from the gut. Subjects without recurrence likely do not harbour the uropathogenic bacteria targeted by PAC-A in the gut.

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