CRANBERRY HEALTH RESEARCH MILESTONES

More than 50 years of research suggests that cranberries play an essential role in promoting health and wellness due to a unique combination of compounds, such as Type-A proanthocyanidins or PACs. These compounds provide an anti-bacterial effect by preventing bacteria from sticking. This unique anti-bacterial effect is one way that cranberry may help lessen the overall number of recurrent urinary tract infections.

Besides helping consumers meet the recommended daily intake of fruit, the nutrient density and health benefits of cranberries make them an important part of a balanced diet and healthy lifestyle.
Clinical research demonstrates that the daily consumption of cranberries may be a nutritional approach to help reduce the number of urinary tract and stomach infections, and therefore the antibiotics used to treat them. The World Health Organization has called antibiotic resistance "one of the greatest challenges for public health today" and it estimates 400,000 people in Europe are infected with a resistant strain of bacteria each year — the Centers for Disease Control and Prevention estimates there are more than 2 million cases in the United States.

A substantial bank of scientific research shows that cranberry can have a positive effect on urinary tract, stomach, oral and cardiovascular health. While the majority of evidence strongly supports the health benefits of cranberry, as with all areas of scientific research, some studies have been inconclusive.
A leader in cranberry research, Ocean Spray is committed to supporting independent studies into the whole-body benefits of cranberry. Some of the cranberry's key research milestones are detailed on the following pages.

Contents

URINARY TRACT HEALTH

October 2018- European Urology Focus **Review**

This review summarized current evidence on nonantibiotic prevention of recurrent UTIs and gives recommendations for patient care. Three new studies and two prior clinical trials investigating the preventative effects of cranberry on UTIs were identified in this review and summarized as current evidence of using cranberries.

Kranz J, Schmidt S, Schneidewind L. Current Evidence on Nonantibiotic Prevention of Recurrent Urinary Tract Infections. Eur Urol Focus. 2018 Oct 3; pii: S2405-4569(18)30278-5. doi: 10.1016/j.euf.2018.09.006

June 2018 –Internal Report **Meta-analysis**

The aim of this review was to evaluate the efficacy of cranberry and risk of UTI in all populations using a systematic review with meta-analysis approach. This study is an expansion of the Fu et al. 2017 study. A total of 20 randomized controlled studies on risk of uncomplicated UTI and some categories of complicated UTI in otherwise healthy populations (e.g., pregnant women, children, and elderly/institutionalized adults). Pooled RR estimates for women (pregnant and non-pregnant) and children with (RR = 0.73 [95% CI: 0.62-0.85]) or without (RR = 0.72 [95% CI: 0.61-0.85]) elderly/ institutionalized adults indicate that cranberry may reduce the risk for UTI recurrence among these populations. Specifically, cranberry-containing products were effective in healthy, non-pregnant women (RR= 0.76 [95% CI: 0.63-0.91]) and children (RR = 0.58 [95% CI: 0.41-0.83]), but not in healthy, pregnant women (RR = 0.87 [95% CI: 0.37-2.04]) and elderly/institutionalized adults (RR =0.81 [95% CI: 0.48-1.35]).

October 2017 – Journal of Nutrition **Meta-analysis**

This meta-analysis assessed the effect of cranberry on the risk of UTI recurrence in otherwise healthy women. Randomized controlled trials conducted in generally healthy nonpregnant women with a history of UTI were included in the meta-analysis. Results of the analysis showed that cranberry reduced the risk of UTI by 26% (pooled risk ratio: 0.74; 95% CI: 0.55, 0.98; I2 = 54%). Risk of bias indicated that 2 studies had high loss to follow-up or selective outcome reporting. Overall, the studies were relatively small, with only 2 having >300 participants. These results suggest that cranberry may be effective in preventing UTI recurrence in generally healthy women.

Fu Z, Liska D, Talan D, Chung M. Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. J Nutr 2016; 147(12):2282-2288.

March 2017 –Journal of Urology **Review**

This systematic review, which complies with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement, was done as a meta-analysis and trial sequential analysis of clinical trials. The findings clearly showed the potential use of cranberries for the clinical condition of urinary tract infection. Cranberry products significantly reduced the incidence of urinary tract infections as indicated by the weighted risk ratio (0.6750, 95% CI 0.5516-0.7965, p <0.0001). The results of subgroup analysis demonstrated that patients at some risk for urinary tract infections were more susceptible to the effects of cranberry ingestion. The results of the current study could be used by physicians to recommend cranberry ingestion to decrease the incidence of urinary tract infections, particularly in individuals with recurrent urinary tract infections. This would also reduce the administration of antibiotics, which could be beneficial since antibiotics can lead to the worldwide emergence of antibiotic resistant microorganisms.

Luís Â, Domingues F, Pereira L. Can Cranberries Contribute to Reduce the Incidence of Urinary Tract Infections? A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Clinical Trials. J Urol. 2017;198(3):614-621. doi: 10.1016/j.juro.2017.03.078. Epub 2017 Mar 10.

June 2016 –American Journal of Clinical Nutrition **Clinical Trial**

Researchers investigated the effect of daily cranberry juice consumption on episodes of clinical UTIs over a 24 wk period. Results indicated that the primary outcome of UTI incidence density was significantly reduced: there were 39 investigator-diagnosed episodes of clinical UTI in the cranberry group compared with 67 episodes in the placebo group (antibiotic use-adjusted incidence rate ratio: 0.61; 95% CI: 0.41, 0.91; P = 0.016), indicating that cranberry is a useful strategy for reducing recurrent clinical UTI episodes and antibiotic use that is associated with UTI treatment.

Maki KC, Kaspar KL, Khoo C, Derrig LH, Schild AL, Gupta K. Consumption of a cranberry juice beverage lowered the number of clinical urinary tract infection episodes in women with a recent history of urinary tract infection. Am J Clin Nutr 2016; 103(6), 1434-1442.

May 2016 –Advances in Nutrition **Review**

Meta-analyses on cranberry and UTI prevention have reported conflicting conclusions. This article explores the methodological differences that contributed to these disparate findings. In the 2 most comprehensive systematic reviews, heterogeneity was handled differently, leading to an I(2) of 65% in one and 43% in the other. Most notably, the populations influencing the conclusions varied. Because women with recurrent UTIs are the group to whom most recommendations regarding cranberry consumption is directed, inclusion of other groups in the efficacy assessment could influence clinical practice quality. Therefore, conclusions on cranberry and UTIs should consider differences in results across various populations studied when interpreting results from meta-analyses.

Liska DJ, Kern HJ, Maki KC. Cranberries and the preventionof urinary tract infections: How can the same evidence lead to conflicting advice? Adv Nutr 2016; 7(3): 498-506.

December 2015 –Annals Pharmacotherapy **Review**

Researchers evaluated existing data regarding the use of cranberry products for the prevention of urinary tract infections (UTIs) in pediatric patients. They determined that cranberry appears effective for the prevention of UTIs in otherwise healthy children and is at least as effective as antibiotics in children with underlying urogenital abnormalities.

Durham SH, Stamm PL, Eiland LS. Cranberry Products for the Prophylaxis of Urinary Tract Infections in Pediatric Patients. Ann Pharmacother. 2015 Dec;49(12):1349-56.

September 2015 – Journal of Agricultural and Food Chemistry **Ex vivo/anti-adhesion**

A group of Germen scientist from University of Münster investigated the anti-adhesion activity of human urine after consuming cranberry extracts and they found out a time-dependent significant inhibition of 40-50% bacterial adhesion of type I UPEC to human T24 bladder cells. They further identified that non-PACs fraction of cranberries exerted this anti-adhesion activity by interaction with mannose-sensitive type 1 fimbriae of UPEC.

Rafsanjany N, Senker J, Brandt S, Dobrindt U, Hensel A. n Vivo Consumption of Cranberry Exerts ex Vivo Antiadhesive Activity against FimH-Dominated Uropathogenic Escherichia coli: A Combined in Vivo, ex Vivo, and in Vitro Study of an Extract from Vaccinium macrocarpon. J Agric Food Chem. 2015 Oct 14;63(40):8804-18.

July 2015- Phytotherapy Research **Clinical Trial**

In this randomized, controlled clinical trial, 500 mg of whole cranberry powder was administered daily to healthy women with recurrent UTIs for 6 months. The researchers found that UTIs were fewer in cranberry vs. placebo [10.8% vs. 25.8%]; cranberry group experienced a longer time to first UTI than the placebo group. Results of this study showed that intake of 500mg of cranberry fruit powder for 6months was associated with a reduction in recurrent UTIs. These data provide encouraging evidence for the protective effect of whole cranberry (peel, seeds, pulp) in women with a medical history of recurrent UTIs

Jitka Vostalova, Ales Vidlar, Vilim Simanek, Adela Galandakova, Pavel Kosina, Jan Vacek, Jana Vrbkova, Benno F. Zimmermann, Jitka Ulrichova and Vladimir Student. Are High Proanthocyanidins Key to Cranberry Efficacy in the Prevention of Recurrent Urinary Tract Infection? Phytother Res. 2015 Oct;29(10):1559-67.

June 2015 – Anales de pediatría (Barc) **Clinical Trial**

Cranberry prophalaxis for recurrent UTIs in adults is proven to be safe, but few data exists on safety and efficacy for younger populations. Results from this study confirm that cranberry is safe and effective in the prophylaxis of

recurrent urinary tract infection in infants and children. With the doses used, their efficiency is not less than that observed for the antibiotic trimethoprim among children over 1 year-old.

Fernández-Puentes V, Uberos J, Rodríguez-Belmonte R, Nogueras-Ocaña M, Blanca-Jover E, Narbona-López E. Efficacy and safety profile of cranberry in infants and children with recurrent urinary tract infection. An Pediatr (Barc). 2015 Jun;82(6):397-403.

April 2015 – American Journal Obstetrics and Gynecology **Clinical Trial**

The risk of urinary tract infection (UTI) among women undergoing elective gynecological surgery during which a catheter is placed is high: 10-64% following catheter removal. Researchers at the University of Michigan conducted the first randomized, double-blind, placebo-controlled trial of the therapeutic efficacy of cranberry juice capsules in preventing UTI after surgery. Results indicated that among women undergoing elective benign gynecological surgery involving urinary catheterization, the use of cranberry extract capsules during the postoperative period reduced the rate of UTI by half.

Foxman B, Cronenwett AE, Spino C, Berger MB, Morgan DM. Cranberry juice capsules and urinary tract infection after surgery: results of a randomized trial. Am J Obstet Gynecol. 2015 Apr 13. pii: S0002-9378(15)00355-5.

April 2015 – Food and Function **Ex vivo/Anti-adhesion**

This study examined the urinary anti-adhesion activity of low-calorie cranberry extract beverages in a pilot study and a randomized, double-blind, placebo controlled clinical trial. Post-consumption urine from both cranberry treatment groups showed significantly higher ($p < 0.05$) anti-adhesion activity compared to placebo, indicating that acute beverage consumption of cranberry beverages provides ex vivo anti-adhesion activity, which may help to improve urinary tract health.

Kaspar KL, Howell AB, Khoo C. A randomized, double-blind, placebo-controlled trial to assess the bacterial anti-adhesion effects of cranberry extract beverages.Food Funct. 2015 Apr;6(4):1212-7.

May 2014 – Nutrition Research **Ex vivo/Anti-adhesion**

This study investigated the effects of cranberry beverages on indices of oxidative stress, inflammation, and urinary antibacterial adhesion activity in healthy humans. An acute dose of cranberry beverages improved biomarkers of antioxidant status and increased ex vivo urinary bacterial anti-adhesion activity against P-fimbriated Escherichia coli compared with placebo ($P < 0.05$).

Mathison B, Kimble L, Kaspar K, Khoo C, Chew B. Consumption of Cranberry Beverage Improved Endogenous Antioxidant Status and Protected Against Bacteria Adhesion in Healthy Humans: A Randomized, Controlled Trial. Nutr Res. 2014 May;34(5):420-7.

March 2014 –Critical Reviews in Food Science and Nutrition **Review**

Epidemiologic studies indicate that millions of people suffer from recurrent cystitis, a pathology requiring antibiotic prophylaxis and entailing high social costs. Cranberry is a traditional folk remedy for cystitis and, which, in the form of a variety of products and formulations has over several decades undergone extensive evaluation for the management of urinary tract infections (UTI). Analysis of clinical studies and evaluation of the cranberry efficacy/safety ratio in the prevention of UTIs strongly support the use of cranberry in the prophylaxis of recurrent UTIs in young and middle-aged women.

Micali S, Isgro G, Bianchi G, Miceli N, Calapai G, Navarra M. Cranberry and recurrent cystitis: more than marketing? Crit Rev Food Sci Nutr. 2014;54(8):1063-75.

January 2014 – Journal of American Geriatrics Society **Clinical Trial**

In a new study, researchers conducted a clinical trial to evaluate the effects of cranberry capsule supplementation on UTI risk in residents of long-term care facilities No difference in UTI incidence between cranberry and placebo was found in participants with low UTI risk (n = 412). In LTCF residents with high UTI risk at baseline, taking cranberry

capsules twice daily reduces the incidence of clinically defined UTI, although it does not reduce the incidence of strictly defined UTI.

Caljouw MA, et al. Effectiveness of Cranberry Capsules to Prevent Urinary Tract Infections in Vulnerable Older Persons: A Double-Blind Randomized Placebo-Controlled Trial in Long-Term Care Facilities. J Am Geriatr Soc. 2014 Jan;62(1):103-10.

November 2013 – Advances in Nutrition **Review**

Recent observational and clinical studies have raised interest in the potential health effects of cranberry consumption, an association that appears to be due to the phytochemical content of this fruit. Human studies on the health effects of cranberry products have focused principally on urinary tract and cardiovascular health, with some attention also directed to oral health and gastrointestinal epithelia. Evidence suggesting that cranberries may decrease the recurrence of urinary tract infections is important because a nutritional approach to this condition could lower the use of antibiotic treatment and the consequent development of resistance to these drugs.

Blumberg JB, Camesano TA, Cassidy A, Kris-Etherton P, Howell A, Manach C, Ostertag LM, Sies H, Skulas-Ray A, Vita JA. Cranberries and their bioactive constituents in human health. Adv Nutr. 2013 Nov 6;4(6):618-32.

October 2013 – Nutrition Journal **Clinical Trial**

Researchers at the University of Wisconisn investigated if sweetened, dried cranberries (SDC) consumption decreases recurrent UTIs and whether this intervention would alter the heterogeneity, virulence factor (VF) profiles, or numbers of intestinal E. coli. Results indicated a beneficial effect from consuming SDC to reduce the number of UTIs in susceptible women, but no changes in the heterogeneity or VF profiles of E. coli were observed, demonstrating that additional studies are needed to determine the mechanism of action of SDC for reduction of UTIs.

Burleigh AE, Benck SM, McAchran SE, Reed JD, Krueger CG, Hopkins WJ. Consumption of sweetened, dried cranberries may reduce urinary tract infection incidence in susceptible women--a modified observational study. Nutr J. 2013 Oct 18;12(1):139.

August 2013 – Nutrition Research **Review**

This review aimed to summarize the proposed mechanisms of cranberry actions against UTIs and the clinical trials that evaluated the efficacy of supplementing cranberry products in different subpopulations. Cranberry consumption may prevent bacterial adherence to uroepithelial cells or decrease UTI related symptoms by suppressing inflammatory cascades as an immunologic response to bacteria invasion. The existing clinical trials suggest that the beneficial effects of cranberry against UTIs seem to be prophylactic by preventing the development of infections; however, they exert low effectiveness in populations at increased risk for contracting UTIs.

Vasileiou I, Katsargyris A, Theocharis S, Giaginis C. Current clinical status on the preventive effects of cranberry consumption against urinary tract infections. Nutrition Research 2013, 33:595-607.

October 2012 – Journal of Urology **Clinical Trial**

This randomized, double-blind, placebo-controlled trial explored the effect of the consumption of a high proanthocyanidin cranberry juice on urinary tract infection rates in children. After 12 months of follow-up, the average incidence of urinary tract infection in the cranberry group was reduced by 65%, indicating that cranberry juice with high concentrations of proanthocyanidins appears to be effective in the prevention of pediatric nonfebrile urinary tract infections.

Afshar K, Stothers L, Scott H, MacNeily AE. Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. J Urol. 2012 Oct;188(4 Suppl):1584-7.

October 2012 – Cochrane Database Systemic Reviews **Meta-analysis**

In previous meta-analyses, there was some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. The addition of 14 further studies suggests

that cranberry juice is less effective than previously indicated. Although some of small studies demonstrated a small benefit for women with recurrent UTIs, there were no statistically significant differences when the results of a much larger study were included. Cranberry products were not significantly different to antibiotics for preventing UTIs in three small studies. Given the large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products particularly juice, over long periods), and the evidence that the benefit for preventing UTI is small, cranberry juice cannot currently be recommended for the prevention of UTIs. Other preparations (such as powders) need to be quantified using standardised methods to ensure the potency, and contain enough of the 'active' ingredient, before being evaluated in clinical studies or recommended for use.

Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2012 Oct 17;10: CD001321.

September 2012 – Journal of Infection and Chemotherapy **Clinical Trial**

Researchers in Japan examined the UTI relapse rate in adult females after cranberry juice supplementation. Compared to placebo, there were no differences in relapse rates between the groups. However, a subgroup analysis of females aged 50 years or more indicated that women in the cranberry juice group had a lower UTI relapse rate compared to the same age group of women on placebo beverage.

Takahashi S, Hamasuna R, Yasuda M, Arakawa S, Tanaka K, Ishikawa K, Kiyota H, Hayami H, Yamamoto S, Kubo T, Matsumoto T. A randomized clinical trial to evaluate the preventive effect of cranberry juice (UR65) for patients with recurrent urinary tract infection. J Infect Chemother, 2012 Sep 8.

July 2012 – Archives of Internal Medicine **Meta-analysis**

Wang et al., provided a systematic review and meta-analysis of thirteen randomized controlled trials evaluating cranberry-containing products for the prevention of UTI and examine the factors influencing their effectiveness. The researchers reported that the results of the analysis support the conclusion that consumption of cranberry-containing products in certain populations may protect against UTIs.

Wang CH, Fang CC, Chen NC, Liu SS, Yu PH, Wu TY, Chen WT, Lee CC, Chen SC. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 2012 Jul 9;172(13):988-96.

June 2012 – Open Access Journal of Clinical Trials **Clinical Trial**

Cranberry prophylaxis of recurrent urinary tract infection in infants has proven effective in the experimental model of the adult. There are few data on its efficacy, safety and recommended dose in the pediatric population.This study confirms that cranberry is safe and effective in the prophylaxis of recurrent urinary tract infection in infants and children.. The cumulative rate of urinary infection associated with cranberry prophylaxis in children under 1 year was 46% (95% CI; 23-70) in children and 17% (95% CI; 0-38) in girls, effectively at doses inferior to trimethoprim. In children over 1 year-old cranberry was not inferior to trimethoprim, with a cumulative rate of urine infection of 26% (95% CI; 12-41). The cranberry was well tolerated and with no new adverse effects.

Uberos J, Nogueras-Ocana M, Fernandez-Puentes V, Rodriguez-Belmonte R, Narbona-López E, Molina-Carballo A, Munoz-Hoyos A. Cranberry syrup vs trimethoprim in the prophylaxis of recurrent urinary tract infections among children: a controlled trial. Open Access Journal of Clinical Trials 2012:4 31–38.

February 2012 – Clinical Infectious Diseases **Clinical Trial**

Researchers in Finland investigated the effect of a 12 month cranberry juice intervention in children with recurrent UTIs. Although the intervention did not significantly reduce the number of children who experienced a recurrence of UTI, children in the cranberry group had a reduced the number of recurrences and related antimicrobial use.

Salo J, Uhari M, Helminen M, Korppi M, Nieminen T, Pokka T, Kontiokari T. Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trial. Clin Infect Dis. 2012 Feb 1;54(3):340-6.

July 2011 – Archives of Internal Medicine **Clinical Trial**

The increasing prevalence of uropathogens resistant to antimicrobial agents has stimulated interest in cranberries to prevent recurrent urinary tract infections (UTIs). This study investigated the effect of cranberry verus antibiotic prophalaxis for the prevention of recurrent UTIs. After 12 months trial antiobiotics were found to be more effective than cranberry capsules to prevent recurrent UTIs, at the expense of emerging antibiotic resistance.

Beerepoot, MAJ et al., Cranberries vs Antibiotics to Prevent Urinary Tract Infections: a Randomized Double-Blind Noninferiority Trial in Premenopausal Women. Archives of Internal Medicine, 2011. 171(14): p. 1270-1278.

2008 – 2011: U.S. GOVERNMENT FUNDED STUDIES

The U.S. government funded a project through NIH/NCCAM titled "Cranberry and Urinary Tract Infection". The purpose of the initiative was to support basic and clinical research on the role of cranberry in the prevention and treatment of urinary tract infections (UTIs). Preference was given to clinical trials designed to determine the efficacy of cranberry in the prevention and/or treatment of UTI. Four clinical trials were funded, two of which have been completed and two are pending.

In the first randomized controlled pilot study published in October 2008, Dr. Wing at the University of California, department of Obstetrics and Gynecology compared the effects of daily cranberry juice cocktail to those of placebo during pregnancy on a marker for and on urinary tract infections. There was a 57% and 41% non-significant reduction in the frequency of bacteria in the urine and all urinary tract infections, respectively, in the multiple daily dosing cranberry juice cocktail groups. The data suggests there may be a protective effect of cranberry ingestion against urinary tract infections during pregnancy.1 In addition, a significant difference in interleukin (IL)-6 was found in the multiple daily cranberry dosing groups compared with placebo.2

The second double-blind, placebo-controlled clinical trial published in January 2011 by Dr. Barbosa-Cesnik evaluated the effect of cranberry juice on risk of recurring UTIs among 319 college women. The researchers report those drinking cranberry juice twice daily did not experience a decrease in the incidence of a second UTI compared with those drinking a placebo.3

The third randomized controlled trial published in 2012 by Dr. Stapleton compared the time to UTI and the rates of asymptomatic bacteriuria and urinary P-fimbriated Escherichia coli during a 6-month period in women ingesting cranberry vs placebo juice daily. The researchers conclude cranberry juice did not significantly reduce UTI risk compared with placebo. However, the potential protective effect they observed is consistent with previous studies and warrants confirmation in larger, well-powered studies of women with recurrent UTI. The concurrent reduction in urinary P-fimbriated E coli strains supports the biological plausibility of cranberry activity.4

1. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy. Journal of Urology 2008; 180:1367-1372.

2 .Wing DA, Rumney PJ, Leu SY, Zaldivar F. Comparison of Urinary Cytokines after Ingestion of Cranberry Juice Cocktail in Pregnant Subjects: A Pilot Study. American Journal of Perinatology 2010; 27:137-142.

3. Barbosa-Cesnik C, Brown MB, Buxton M, Zhang L, DeBusscher J, Foxman B. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clinical Infectious Diseases 2011; 52:23-30.

4. Stapleton AE, Dziura J, Hooton TM, Cox ME, Yarova-Yarovaya Y, Chen S, Gupta K. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. Mayo Clin Proc. 2012 Feb;87(2):143-50.

April 2010 – BMC Infectious Diseases **Ex vivo/Anti-adhesion**

Dr. Howell, a researcher at Rutgers University, used two separate bioassays (a mannose-resistant hemagglutination assay and an original new human T24 epithelial cell-line assay) to assess the ex-vivo urinary bacterial anti-adhesion activity on urine samples collected from 32 volunteers from Japan, Hungary, Spain and France in a randomized, double-blind versus placebo study. An in vivo Caenorhabditis elegans model was used to evaluate the influence of cranberry regimen on the virulence of E. coli strain. The researchers conclude that administration of PAC-standardized cranberry powder at dosages containing 72mg of PAC per day may offer some protection against bacterial adhesion and virulence in the urinary tract.

Howell AB, Botto H, Combescure C, Blanc-Potard AB, Gausa L, Matsumoto T, Tenke P, Sotto A, Lavigne JP. Dosage effect on uropathogenic Escherichia coli anti-adhesion activity in urine following consumption of cranberry powder standardized for proanthocyanidin content: a multicentric randomized double blind study. BMC Infect Dis. 2010 Apr 14;10:94.

November 2009 – Scandinavian Journal of Urology and Nephrology **Clinical Trial**

This randomized controlled pilot study conducted at Catholic University in Rome Italy, compared the effects of daily cranberry juice cocktail to those of Lactobacillus in children with recurrent urinary tract infections. There were 34 episodes of UTIs: 5/27 (18.5%) in the cranberry juice group, 11/26 (42.3%) in the Lactobacillus group and 18/27 (48.1%) in the control group. These results suggested that daily consumption of concentrated cranberry juice can significantly prevent the recurrence of symptomatic UTIs in children.

Ferrara P, Romaniello L, Vitelli O, Gatto A, Serva M, Cataldi L. Cranberry juice for the prevention of recurrent urinary tract infections: A randomized controlled trial in children. Scandinavian Journal of Urology and Nephrology 2009; 43:369-372.

February 2009 – Journal of Antimicrobial Chemotherapy **Review**

Researchers from the University of Dundee in Scotland compared the effectiveness of cranberry extract with a low-dose of antibiotic in the prevention of recurrent urinary tract infections (UTIs) in older women. There were no differences in proportions relative risk and time to first recurrence of UTI between the cranberry and antibiotic groups. Therefore, antibiotic had a very limited advantage over cranberry in the prevention of recurrent UTIs in older women and had more adverse effects. Our findings will allow older women with recurrent UTIs to weigh up with their clinicians the inherent attractions of a cheap, natural product like cranberry extract whose use does not carry the risk of antimicrobial resistance or super-infection with Clostridium difficile or fungi.

McMurdo MET, Argo I, Phillips G, Daly F, Davey P. Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women. Journal of Antimicrobial Chemotherapy 2009; 63(2):389-395.

January 2009 – Cochrane Database Systematic Review **Meta-analysis**

Cranberries have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs), therefore an assessment of the effectiveness of cranberry products in preventing UTIs in susceptible populations is warrented. In this meta-anlysis, cranberry products significantly reduced the incidence of UTIs at 12 months (RR 0.65, 95% CI 0.46 to 0.90) compared with placebo/control. Cranberry products were more effective reducing the incidence of UTIs in women with recurrent UTIs, than elderly men and women or people requiring catheterisation. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules). Further properly designed studies with relevant outcomes are needed.

Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews 2009; Issue 1.

ADDITIONAL RESEARCH REFERENCES

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Cai T, Caola I, Tessarolo F, Piccoli F, D'Elia C, Caciagli P, Nollo G, Malossini G, Nesi G, Mazzoli S, Bartoletti R. Solidago, orthosiphon, birch and cranberry extracts can decrease microbial colonization and biofilm development in indwelling urinary catheter: a microbiologic and ultrastructural pilot study. World J Urol. 2014 Aug;32(4):1007-14.

Dieter AA. Cranberry capsules (2 taken twice daily for an average 38 days) reduce the risk of postoperative urinary tract infection in women undergoing benign gynaecological surgery involving intraoperative catheterisation. Evid Based Med. 2015 Aug;20(4):137.

Barnoiu OS, Sequeira-García Del Moral J, Sanchez-Martínez N, Díaz-Molina P, Flores-Sirvent L, Baena-González V. American cranberry (proanthocyanidin 120 mg): its value for the prevention of urinary tracts infections after ureteral catheter placement. Actas Urol Esp. 2015 Mar;39(2):112-7.

Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014 Mar;28(1):1-13.

Greenberg JA, Newmann SJ, Howell AB. Consumption of sweetened dried cranberries versus unsweetened raisins for inhibition of uropathogenic Escherichia coli adhesion in human urine: a pilot study. Journal of Alternative and Complementary Medicine 2005; 11:875-878.

Howell AB, Reed JD, Krueger CG, Winterbottom R, Cunningham DG, Leahy M. A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. Phytochemistry 2005; 66:2281-2291.

Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. British Medical Journal 2001; 322:1571-1575.

Ledda A, Bottari A, Luzzi R, Belcaro G, Hu S, Dugall M, Hosoi M, Ippolito E, Corsi M, Gizzi G, Morazzoni P, Riva A, Giacomelli L, Togni S. Cranberry supplementation in the prevention of non-severe lower urinary tract infections: a pilot study. Eur Rev Med Pharmacol Sci. 2015 Jan;19(1):77-80.

Madden GR, Argraves SM, Van Ness PH, Juthani-Mehta M. Antibiotic Susceptibility of Urinary Isolates in Nursing Home Residents Consuming Cranberry Capsules Versus Placebo. Infect Control Hosp Epidemiol. 2015 Mar;36(3):356-357.

Stothers LA. randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. The Canadian Journal of Urology 2002; 9:1558-1562.

Walker EB, Barney DP, Mickerlsen JN, Walton RJ, Mickelsen RAJr. Cranberry concentrate: UTI prophylaxis. Journal of Family Practice 1997; 45:167-168.

Williams K, South M. Pros and cons of antibiotics for preventing recurrent urinary tract infection. J Paediatr Child Health. 2013 Jan;49(1):75-7.

Wing DA, Rumney PJ, Hindra S, Guzman L, Le J, Nageotte M. Pilot Study to Evaluate Compliance and Tolerability of Cranberry Capsules in Pregnancy for the Prevention of Asymptomatic Bacteriuria. J Altern Complement Med. 2015 Nov;21(11):700-6

GUT HEALTH

September 2018 — Journal of Nutritional Biochemistry **Clinical**

In a randomized, double-blind, cross-over, placebo controlled human trial, 11 healthy adults consumed for 5 days each a control diet (animal-based diet plus 30 g/day placebo powder) and a cranberry diet (animal-based diet plus 30 g/day freeze-dried whole cranberry powder). As compared to the post-intervention phase of control diet, the cranberry diet modified 9 taxonomic clades, including a decrease in the abundance of Firmicutes and increase in Bacteroidetes. Further, the cranberry diet attenuated control diet-induced increase in secondary bile acids and decrease in short-chain fatty acids, and increased urinary anthocyanins and bacterially derived phenolic acids.

Rodríguez-Morató J, Matthan NR, Liu J, de la Torre R, Chen CO. Cranberries attenuate animal-based diet-induced changes in microbiota composition and functionality: a randomized crossover controlled feeding trial. J Nutr Biochem. 2018 Sep 8;62:76-86. doi: 10.1016/j.jnutbio.2018.08.019.

December 2017 — Molecular Metabolism **Animal**

In this study, mice were fed with either a rodent chow diet or a High Fat-High Sucrose (HFHS) diet for 13 weeks to induce obesity and then treated either with cranberry extract (CE; 200 mg/kg/day) or vehicle for 8 additional weeks. CE did not reverse weight gain or fat mass accretion in Chow- or HFHS-fed mice. However, HFHS plus CE fully reversed hepatic steatosis and this was linked to upregulation of genes involved in lipid catabolism and downregulation of several pro-inflammatory genes in the liver. These findings were associated with improved glucose tolerance and normalization of insulin sensitivity in HFHS plus CE mice. The gut microbiota of HFHS plus CE mice was characterized by lower Firmicutes to Bacteroidetes ratio and a drastic expansion of Akkermansia muciniphila and, to a lesser extent, of Barnesiella spp, as compared to HFHS controls.

Anhe FF, Nachbar RT, Varin TV, Vilela V, Dudonne S, Pilon G, Fournier M, Lecours MA, Desjardins Y, Roy D, Levy E, Marette A. A polyphenol-rich cranberry extract reverse insulin resistance and hepatic steatosis independently of body weight loss. Mol Metab. 2017 Dec;6(12):1563-1573.

November 2017 — European Journal of Nutrition **Animal**

In this study, mice were fed normal chow or high fat diet (HFD), and were administered either cranberry extrat (CRX; 200 mg/kg) alone or in combination with isomalto-oligosaccharides (IMOs; 1 g/kg). Co-supplementation of CRX and IMOs significantly improved cecal shrt chain fatty acids, selected butyrate-producing bacteria (clostridial cluster XIVa bacteria) in HFD-fed mice. The combination also significantly improved gut beneficial bacterial abundance, gut histology and related changes (colon mucin production, gut permeability). It also prevented HFD-induced systemic and tissue inflammation, glucose intolerance and systemic obesity-associated metabolic changes in adipose tissue and liver.

Singh DP, Singh S, Bijalwan V, Kumar V, Khare P, Baboota RK, Singh P, Boparai RK, Singh J, Kondepudi KK, Chopra K, Bishnoi M. Co-supplementation of isomalto-oligosaccharides potentiates metabolic health benefits of polyphenol-rich cranberry extract in high fat diet-fed mice via enhanced gut butyrate production. Eur J Nutr. 2017 Nov 10. doi: 10.1007/s00394-017-1561-5. [Epub ahead of print]

June 2017—Applied and Environmental Microbiology **In vitro**

In this study, effects of cranberry-derived xyloglucans on bacterial growth and energy metabolism were tested under plate culture condition. Interestingly, the Bifidobacterium longum (B. longum) strain that efficiently utilizes xyloglucans secrete 2.0-2.5 moles acetate:lactate, indicating a hexose fermentations shift during xyloglucan metabolism. Accordingly, this metabolic shift is characterized by increased acetate and formate production at the expense of lactate. Certain sugar utilizing enzymes and membrane transporter proteins are upregulated. Finally, syntrophic interactions occurred with strains that utilize carbohydrate products derived from initial degradation from a heterologous bacterium.

Özcan E, Sun J, Rowley DC, Sela DA. A Human Gut Commensal Ferments Cranberry Carbohydrates To Produce Formate. Appl Environ Microbiol. 2017 Sep 1; 83(17): e01097-17. doi: 10.1128/AEM.01097-17.

October 2016 — Journal of Research in Pharmacy Practice **Clinical**

In this study, H. pylori test (urea breath test; UBT) positive patients with peptic ulcer diseases were randomized into two groups: Group A: a 14-day standard medication therapy; Group B: a 14-day standard medication therapy with 500 mg cranberry capsules twice a day. Another UBT was performed for eradication assessment 6 weeks after the completion of the treatment. Two hundred adult patients completed study protocol. H. pylori eradication was achieved in 74% in Group A (medication alone without cranberry) and 89% in Group B (medication with cranberry) (P = 0.042).

Seyyedmajidi M, Ahmadi A, Hajiebrahimi S, Seyedmajidi S, Rajabikashani M, Firoozabadi M, Vafaeimanesh J. Addition of cranberry to proton pump inhibitor-based triple therapy for Helicobacter pylori eradication. J Res Pharm Pract. 2016;5:248-51.

August 2015 – PharmaNutrition **Animal**

In this study, mice were fed with a high fat high sucrose diet with addition of cranberry extract (200mg/kg/d) or probiotic strain Bacillus subtilis (1×10^9/mL) daily for 9 weeks. A total of 22 circulating metabolites were identified, mainly microbial degradation products of native cranberry phenolic compounds. Plasma concentration of 3

microbial metabolites was significantly increased with the cranberry extract/Probiotics co-treatment: *p*-coumaric acid, *m*-coumaric acid and *p*-hydroxybenzoic acid (+53%, +103% and +70% respectively). Associated to this modulation, we reported significant differences in the proportion of *Barnesiella* and *Oscillibacter* genera in cranberry extract/Probiotics treated mice in comparison with control animals.

Dudonné S., Varin T.V., Forato Anhê F., Dubé P., Roy D., Pilon G. Modulatory effects of a cranberry extract co-supplementation with Bacillus subtilis CU1 probiotic on phenolic compounds bioavailability and gut microbiota composition in high-fat diet-fed mice. PharmaNutrition. 2015;3:89–100.

June 2015 – Gut **Animal**

In this study, mice were fed either a chow or a high-fat high-sugar diet (HFHS). HFHS-fed mice were gavaged daily either with water or cranberry extract (CE) for 8 weeks. CE exerted beneficial metabolic effects through improving HFHS diet-induced features of the metabolic syndrome, which was associated with a proportional increase in Akkermansia spp.

Anhê FF, Roy D, Pilon G, Dudonné S, Matamoros S, Varin TV, Garofalo C, Moine Q, Desjardins Y, Levy E, Marette A. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. Gut. 2015 Jun;64(6):872-83

January 2015 – Food Chemistry **Animal**

In this experimental model of inflammatory bowel disease (IBD), shortening of colon length, colonic myeloperoxidase activity and production of pro-inflammatory cytokines were attenuated in animals fed dried cranberries compared to the controls. These results suggest that cranberries can be applied to prevent and reduce the symptoms of IBD.

Xiao X, Kim J, Sun Q, Kim D, Park CS, Lu TS, Park Y. Preventive effects of cranberry products on experimental colitis induced by dextran sulphate sodium in mice. Food Chem. 2015 Jan 15;167:438-46.

November 2014 – Molecular Nutrition & Food Research **In vitro**

Procyanidins, both B-type and A-type can be degraded by human gut microbiota and the profile of microbial metabolites derived from A-type procyanidins differ from those of B-type, possibly explaining the bioactivity of cranberry A-type procyanidins.

Ou K, Sarnoski P, Schneider KR, Song K, Khoo C, Gu L .Microbial catabolism of procyanidins by human gut microbiota. Mol Nutr Food Res. 2014 Nov;58(11):2196-205.

June 2013 – Journal of Food Science **In vitro**

This in vitro study suggests that cranberries do not lose their antioxidant ability when passing through the GI tract, and specifically, digested cranberries may serve to enhance cytoprotective effects in intestinal cells by reducing potential damage caused by free radicals and ROS derived from other food sources.

Slemmer JE, Livingston-Thomas JM, Gottschall-Pass KT, Sweeney MI. Cranberries and wild blueberries treated with gastrointestinal enzymes positively modify glutathione mechanisms in Caco-2 cells in vitro. J Food Sci. 2013 Jun;78(6):H943-7.

May 2013 – Journal of Parenteral and Enteral Nutrition **Animal**

This study shows that, in mice, administration of elemental enteral nutrition produces lower levels of the Th2 stimulating cytokine IL-13, lower goblet cells number and size, and lowers luminal mucin levels. Cranberry PAC addition to the diet, at physiologic doses, attenuates these changes and likely normalizes mucosal integrity. This suggests that a non-nutritional dietary component such as PAC may influence health without being absorbed from the gastrointestinal tract.

Pierre JF, Heneghan AF, Feliciano RP, Shanmuganayagam D, Roenneburg DA, Krueger CG, Reed JD, Kudsk KA. Cranberry proanthocyanidins improve the gut mucous layer morphology and function in mice receiving elemental enteral nutrition. JPEN J Parenter Enteral Nutr. 2013 May-Jun;37(3):401-9.

April 2012 – Current opinion in biotechnology **Review**

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 and in vivo data partially support these beneficial effects in urinary tract infections, in H. pylori infections in women and in oral health. There is a need for further studies focussing on the active cranberry component as supplement for food and other products especially where whole juice or powder cannot be used.

Shmuely H, Ofek I, Weiss EI, Rones Z, Houri-Haddad Y. Cranberry components for the therapy of infectious disease. Curr Opin Biotechnol. 2012 Apr;23(2):148-52.

December 2008 – *Journal of Gastroenterology and Hepatology* **In vitro**

Researchers at Tokai University School of Medicine in Japan report that cranberry extract inhibited *H. pylori* proliferation and it is suggested that polyphenols are responsible for this action. The morphological analysis used for this study suggested that cranberry induces *H. pylori* to develop a coccoid form, thereby inhibiting its growth. *H. pylori* binding to the stomach lining is an important step in the progression of events leading to some ulcers.

Matsushima M, SuzukiT, Masui A, Kasai K, Kouchi T, Takagi A, Shirai T, Mine T. Growth inhibitory action of cranberry on *Helicobacter pylori*. *Journal of Gastroenterology and Hepatology* 2008; 23:S175-S180.

May 2008 – Nutrition **Clinical**

At the University of Chile, a multicentric, randomized, controlled, double-blind trial was carried out in 295 asymptomatic children to evaluate whether regular intake of cranberry juice and the probiotic *Lactobacillus johnsonii* La1 (La1) may result in an additive or synergistic inhibition of *H. pylori*. The researchers' results suggest that regular intake of cranberry juice or La1 may be useful in the management of asymptomatic children colonized by *H. pylori*. However, no synergistic inhibitory effects on *H. pylori* colonization were observed when both foodstuffs were simultaneously consumed.

Gotteland M, Andrews M, Toledo M, Munoz L, Caceres P, Anzini A, Witting E, Speisky H, Salazar G. Modulation of *Helicobacter pylori* colonization with cranberry juice and *Lactobacillus johnsonii* La1 in children. *Nutrition* 2008; 24:421-426.

June 2007 – Molecular Nutrition and Food Research **Clinical**

In a double-blind, randomized clinical study performed by researchers at Tel Aviv University, Israel, the ability of cranberry juice to potentiate triple antibiotic therapy for *H. pylori* was tested. The results suggested that cranberry juice with triple therapy was significantly more effective in improving the rate of *H. pylori* eradication in women than triple therapy alone. No significant difference was seen in males.

Shmuely H, Yahav J, Samra Z, Chodick G, Koren R, Niv Y, Ofek I. Effect of cranberry juice on eradication of *Helicobacter pylori* in patients treated with antibiotics and a proton pump inhibitor. *Molecular Nutrition and Food Research* 2007; 51:746-751.

December 2005 – Clinical Nutrition **Clinical**

In a clinical study to evaluate the effect of cranberry juice on colonic bacterial flora in children, researchers at the University of Turku, Finland, report no differences in fecal fatty acid composition compared with control. This suggests that cranberry juice cocktail does not adversely affect the healthy bacterial GI flora.

Kontiokari T, Salo J, Eerola E, Uhari M. Cranberry juice and bacterial colonization in children-a placebo-controlled randomized trial. *Clinical Nutrition* 2005; 24:1065-1072.

March 2005 – Helicobacter **Clinical**

This clinical study performed at the School of Oncology, Peking University, found that daily consumption of cranberry juice showed a modest but significant attenuation of *H. pylori* in humans, suggesting that regular consumption of cranberry juice may help to retard *H. pylori* infection in adults.

Zhang L, Ma J, Pan K, Go VLW, Chen J, You W. Efficacy of cranberry juice on *Helicobacter pylori* Infection: a double-blind, randomized placebo-controlled trial. *Helicobacter* 2005; 10:139-145.

April 2005 – *Biofactors* **Review**

A review of the antibacterial effect of berries on GI pathogens is presented which includes a discussion of the unique property of cranberry PACs in the context of anti-adhesion of bacteria.

Leitoao DPS, Polizello ACM, Ito IY, Spadaro ACC. Antibacterial screening of anthocyanic and proanthocyanic fractions from cranberry juice. *Journal of Medicinal Food* 2005; 8:36-40.

December 2004 – Diagnostic microbiology and infectious disease **In vitro**

In this in vitro study, the sensitivity of a large number of antibiotic-resistant and nonresistant H. pylori isolates to the antiadhesion effect of a high-molecular-mass, nondialysable constituent of cranberry juice was assessed. In two thirds of the isolates, adhesion to the gastric cells was inhibited by 0.2 mg/mL of the nondialysable material. In certain cases (16%), isolates were resistant to both the nondialysable material and metronidazole These data suggest that a combination of antibiotics and a cranberry preparation may improve H. pylori eradication.

Shmuely H, Burger O, Neeman I, Yahav J, Samra Z, Niv Y, Sharon N, Weiss E, Athamna A, Tabak M, Ofek I. Susceptibility of Helicobacter pylori isolates to the antiadhesion activity of a high-molecular-weight constituent of cranberry. Diagn Microbiol Infect Dis. 2004 Dec;50(4):231-5.

January 2002 - Critical reviews in food science and nutrition **In vitro**

A high-molecular-weight constituent of cranberry juice was found to inhibit the sialyllactose specific adhesion of Helicobacter pylori strains to immobilized human mucus, erythrocytes, and cultured gastric epithelial cells. Different isolates of H. pylori differ in their affinity to the cranberry juice constituent. Cranberry juice may also inhibit adhesion of bacteria to the stomach in vivo, and may prove useful for the prevention of stomach ulcer that is caused by H. pylori.

Burger O, Weiss E, Sharon N, Tabak M, Neeman I, Ofek I. Inhibition of Helicobacter pylori adhesion to human gastric mucus by a high-molecular-weight constituent of cranberry juice. Crit Rev Food Sci Nutr. 2002;42(3 Suppl):279-84.

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Majeed M, Nagabhushanam K, Arumugam S, Natarajan S, Majeed S, Pande A, Beede K, Ali F. Cranberry seed fibre: A promising prebiotic fibre and its fermentation by the probiotic bacillus coagulans mtcc 5856. Int J Food Sci Technol. 2018;53:1640-1647.

Bekiares N, Krueger CG, Meudt JJ, Shanmuganayagam D, Reed JD. Effect of Sweetened Dried Cranberry Consumption on Urinary Proteome and Fecal Microbiome in Healthy Human Subjects. OMICS. 2018 Feb;22(2):145-153.

Anhê FF, Pilon G, Roy D, Desjardins Y, Levy E, Marette A. Triggering Akkermansia with dietary polyphenols: a new weapon to combat the metabolic syndrome? Gut Microbes. 2016 Feb 22:0.

Denis MC, Desjardins Y, Furtos A, Marcil V, Dudonné S, Montoudis A, Garofalo C, Delvin E, Marette A, Levy E. Prevention of oxidative stress, inflammation and mitochondrial dysfunction in the intestine by different cranberry phenolic fractions. Clin Sci (Lond). 2015 Feb;128(3):197-212.

Ramirez-Hernandez A, Rupnow J, Hutkins RW. Adherence Reduction of Campylobacter jejuni and Campylobacter coli Strains to HEp-2 Cells by MannanOligosaccharides and a High-Molecular-Weight Component of Cranberry Extract. J Food Prot. 2015 Aug;78(8):1496-505.
Anhê FF, Varin TV, Le Barz M, Desjardins Y, Levy E, Roy D, Marette A. Gut Microbiota Dysbiosis in Obesity-Linked Metabolic Diseases and Prebiotic Potential of Polyphenol-Rich Extracts. Curr Obes Rep. 2015 Dec;4(4):389-400.

Popov SV, Markov PA, Nikitina IR, Petrishev S, Smirnov V, Ovodov YS. Preventative effect of a pectic polysaccaride of the common cranberry *Vaccinium oxycoccos* L. on acetic acid-induced colitis in mice. *World Journal of Gastroenterology* 2006; 12:6646-6651.

Leitoao DPS, Polizello ACM, Ito IY, Spadaro ACC. Antibacterial screening of anthocyanic and proanthocyanic fractions from cranberry juice. *Journal of Medicinal Food* 2005; 8:36-40.

Puupponen-Pimia R, Nohynek L, Alakomi HL, Oksman-Caldentey KM. The action of berry phenolics against human intestinal pathogens. *BioFactors* 2005; 23:243-251.

HEART HEALTH

March 2018 – European Journal of Nutrition **Clinical**

In this clinical study, 78 overweight or obese adults consumed 450mL cranberry extract beverage or a placebo beverage acutely or 8 weeks a high polyphenol cranberry beverage was administered acutely versus chronically to overweight but otherwise healthy adults. A single dose improved antioxidant status, while 8 wk of daily consumption reduced cardiovascular disease risk factors by lowering serum insulin, downregulating inflammatory biomarkers C-reactive protein, and increasing HDL cholesterol.

Chew B, Mathison B, Kimble L, McKay D, Kaspar K, Khoo C, Chen CO, Blumberg J. Chronic consumption of a low calorie, high polyphenol cranberry beverage attenuates inflammation and improves glucoregulation and HDL cholesterol in healthy overweight humans: a randomized controlled trial. Eur J Nutr. 2018 Feb 23. doi: 10.1007/s00394-018-1643-z. [Epub ahead of print]

June 2015 – Gut **Animal**

In this study, mice were fed either a chow or a high-fat high-sugar diet (HFHS). HFHS-fed mice were gavaged daily either with water or cranberry extract (CE) for 8 weeks. CE exerted beneficial metabolic effects through improving HFHS diet-induced features of the metabolic syndrome, which was associated with a proportional increase in Akkermansia spp.

Anhê FF, Roy D, Pilon G, Dudonné S, Matamoros S, Varin TV, Garofalo C, Moine Q, Desjardins Y, Levy E, Marette A. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. Gut. 2015 Jun; 64(6):872-83.

February 2015 – The Journal of Nutrition **Clinical**

This double-blind, placebo-controlled, parallel-arm study was conducted in 30 women and 26 men for 8 weeks. Twice daily volunteers consumed 240 mL of Low calorie cranberry juice (LCCJ) or a placebo beverage. Results show that LCJC consumption can improve several risk factors of CVD in adults, including circulating TGs, CRP, glucose, insulin resistance, and diastolic blood pressure.

Novotny JA, Baer DJ, Khoo C, Gebauer SK, Charron CS. Cranberry juice consumption lowers markers of cardiometabolic risk, including blood pressure and circulating C-reactive protein, triglyceride, and glucose concentrations in adults. J Nutr. 2015;45(6):1185-93.

May 2014 – Journal of agricultural and food chemistry **Review**

Epidemiological evidence indicates that the cardiovascular health benefits of diets rich in berries are related to their (poly)phenol content. These findings are supported by small-scale randomized controlled studies (RCTs) that have shown improvements in several surrogate markers of cardiovascular risk such as blood pressure, endothelial function, arterial stiffness, and blood lipids. Although the current evidence is promising, more long-term RCTs are needed.

Rodriguez-Mateos A, Heiss C, Borges G, Crozier A. Berry (poly)phenols and cardiovascular health. J Agric Food Chem. 2014 May 7;62(18):3842-51.

November 2013 – British Journal of Nutrition **Clinical**

In the present study, a randomized clinical trial, the effects of the consumption of reduced-energy cranberry juice containing folic acid for 60 days was assessed in patients with metabolic syndrome (MetS). Results show that patients in the cranberry juice-treated group demonstrated a significant increase in plasma adiponectin levels, while serum homocysteine (Hcys) levels were decreased as well as the levels of oxidative stress.

Simão TN, Lozovoy MA, Simão AN, Oliveira SR, Venturini D, Morimoto HK, Miglioranza LH, Dichi I. Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome. Br J Nutr. 2013 Nov;110(10):1885-94.

January 2013 - Nutrition Research **Clinical**

This 4 weeks double-blind crossover study was performed in 35 abdominally obese men. The changes on Augmentation index (AIx), an index of arterial stiffness, after chronic consumption of cranberry juice cocktail (CJC)

was not significantly different from changes associated with the consumption of the placebo. However, a significant within-group decrease in AIx following CJC consumption was observed and deserves further investigation.

Ruel G, Lapointe A, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Evidence that cranberry juice may improve augmentation index in overweight men. Nutr Res. 2013 Jan;33(1):41-9.

April 2012 – British Journal of Nutrition **Clinical**

This double-blind randomized clinical trial was conducted in 58 type 2 diabetic male patients receiving either 1 cup cranberry juice (CJ) or placebo drink daily for 12 weeks. At the end of 12 weeks, subjects who received CJ showed a significant reduction in serum glucose and apoB and had an increase in apoA-1 and PON-1 activity. These results suggest that consumption of CJ may have a favorable impact in reducing CVD risk factors associated with type 2 diabetes.

Shidfar F, Heydari I, Hajimiresmaiel SJ, Hosseini S, Shidfar S, Amiri F. The effects of cranberry juice on serum glucose, apoB, apoA-I, Lp(a), and Paraoxonase-1 activity in type 2 diabetic male patients. J Res Med Sci. 2012 Apr;17(4):355-60.

March 2012 – *European Journal of Nutrition* **Clinical**

Flammer et al. conducted a clinical trial which showed no significant differences in endothelial function as determined by reactive hyperemia-peripheral arterial tonometry (RH-PAT) scores and circulating EPCs for which both were primary endpoints. In addition, no differences in lipid profiles, oxidized LDL (oxLDL), C-reactive protein, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) or soluble inter-cellular adhesion molecule 1 (ICAM-1) or vascular-cellular adhesion molecule 1(VCAM-1) were observed. However, this study included the measure of circulating endothelial progenitor cells (EPCs) which is evolving as a novel method of assessing the process of the early stages of vascular injury repair. The results showed a significant decreased proportion in circulating EPCs co-expressing osteogenic cell markers. Dr. Lerman recently reported that early coronary atherosclerosis is characterized by an increased proportion in EPCs carrying the osteoblastic marker osteocalcin (OCN), which may mediate abnormal repair and vascular calcification.

Flammer AJ, Martin EA, Gössl M, Widmer RJ, Lennon RJ, Sexton JA, Loeffler D, Khosla S, Lerman LO, Lerman A. Polyphenol-rich cranberry juice has a neutral effect on endothelial function but decreases the fraction of osteocalcin-expressing endothelial progenitor cells. Eur J Nutr. 2012 Mar 2.

May 2011 – *American Journal of Clinical Nutrition* **Clinical**

The researchers completed an acute pilot study with no placebo (n = 15) and a chronic placebo-controlled crossover study that examined the effects of cranberry juice on vascular function in 44 subjects with coronary artery disease. The uncontrolled pilot study suggested an acute benefit; however, no chronic effect on measures of endothelial vasodilator function was found. However, Dohadwala et al. showed that drinking the equivalent of 4 servings of low calorie cranberry beverage daily significantly improved arterial stiffness in cardiovascular patients on stable medication. Arterial stiffness is becoming an important emerging risk factor of cardiovascular disease.

Dohadwala MM, Holbrook M, Hamburg NM, Shenouda SM, Chung WB, Titas M, Kluge MA, Wang N, Palmisano J, Milbury PE, Blumberg JB, Vita JA. Effects of cranberry juice consumption on vascular function in patients with coronary artery disease. Am J Clin Nutr. 2011 May;93(5):934-40.

March 2011 – *Nutrition Research* **Clinical**

Metabolic syndrome is becoming a significant concern for the American population as the number of people with prehypertension, prediabetes, dyslipedemia and other early risk factors of cardiovascular disease continue to increase. In subjects with metabolic syndrome, Basu et al., showed that drinking 2 servings of low calorie CJC (480 mL/day) or placebo (480 mL/day) for 8 weeks significantly improved LDL oxidation and other inflammatory markers suggesting that cranberry polyphenols are bioavailable and may support antioxidant and anti-inflammatory functions in the body.

Basu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. Nutr Res. 2011 Mar;31(3):190-6

April 2010 – *Journal of Agricultural and Food Chemistry*

This *in vitro* study conducted at the William Harvey Research Institute in England suggests that a serving of cranberry juice cocktail each day could be as good for the heart as red wine. Scientists tested cranberry juice cocktail, light cranberry juice cocktail, a California merlot and an Argentine cabernet sauvignon on endothelin-1, a marker of blood vessel dilation/constriction, and found similar changes. These cell studies findings suggest cranberry juice cocktail and red wine may have similar abilities to promote healthy arteries.[1,2]

1. Corder R. Anti-atherosclerotic potential of cranberry juice and red wine: comparable inhibition of endothelin-1 synthesis by cultured endothelial cells. Presented at The 227th ACS National Meeting, Anaheim, CA, March 28-April 1, 2004.

2. Caton PW, Pothecary MR, Lees DM, Khan NQ, Wood EG, Shoji T, Kanda T, Rull G, Corder R. Regulation of Vascular Endothelial Function by Procyanidin-Rich Foods and Beverages. *Journal of Agricultural and Food Chemistry* 2010; 58:4008-4013.

October 2010 – *Journal of Food Science* **Clinical**

In two separate clinical studies, researchers at Winona State University investigated the effect of different cranberry products on the glycemic response of Type 2 diabetics. Results indicated that consumption of aw cranberries and sweetened dried cranberries containing less sugar had a more favorable glycemic and insulinemic response compared to participants who consumed sweetened dried cranberries.[1] Similarly, blood glucose and plasma insulin values were significantly lower in the participants who consumed unsweetened, low-calorie cranberry juice compared to normal-calorie cranberry juice.[2] The researchers concluded that cranberry products containing less sugar may be associated with a more favorable metabolic response in Type 2 diabetics.

1. Wilson T, Luebke JL, Morcomb EF, Carrell EJ, Leveranz MC, Kobs L, Schmidt TP, Limburg PJ, Vorsa N, Singh AP. Glycemic responses to sweetened dried and raw cranberries in humans with type 2 diabetes. *Journal of Food Science* 2010; 75:H218-H223.

2. Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N. Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. *Journal of Food Science* 2008; 73:H241-H245.

December 2009 - *Journal of the American College of Nutrition* **Clinical**

This study showed that low-calorie cranberry juice cocktail supplementation in abdominally obese men was able to significantly decrease Matrix metalloproteinase (MMP)-9, which has been implicated in the development of hypertension and atherosclerotic plaque vulnerability to rupture, an important step in the etiology of CVD.

Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Plasma matrix metalloproteinase (MMP)-9 levels are reduced following low-calorie cranberry juice supplementation in men. J Am Coll Nutr. 2009 Dec;28(6):694-701.

December 2008 – *Diabetic Medicine* **Clinical**

Researchers at Taichung Veterans General Hospital in Taiwan conducted a clinical study to examine the effect of cranberry extract ingestion on lipid profiles in Type 2 diabetic patients taking oral glucose-lowering drugs. The researchers conclude cranberry supplements are effective in reducing atherosclerotic cholesterol profiles, including LDL cholesterol and total cholesterol levels, as well as total:HDL cholesterol ratio, and have a neutral or no effect on glycemic control and LDL oxidation in Type 2 diabetic subjects taking oral glucose-lowering agents.

Lee IT, Chan YC, Lin CW, Lee WJ, Sheu WH. Effect of cranberry extracts on lipid profiles in subjects with type 2 diabetes. *Diabetic Medicine* 2008; 25:1473-1477.

February 2008 – *British Journal of Nutrition* **Clinical**

Continuing previous research, Ruel and colleagues at Laval University report that daily consumption of light cranberry juice drink is associated with decreases in oxidation of LDL cholesterol and cell adhesion molecules (ICAM-1 & VCAM-1) in men.

Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men. Br J Nutr. 2008 Feb;99(2):352-9.

August 2006 – *British Journal of Nutrition* **Clinical**

In this study, Ruel et al. showed that daily CJC consumption of low-calorie cranberry juice cocktail was associated with an increase in plasma HDL-cholesterol concentrations in abdominally obese men. The effect was observed after the consumption of 250 mL CJC/d and plateaued when subjects consumed 500 mL CJC/d.

Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Favourable impact of low-calorie cranberry juice consumption on plasma HDL-cholesterol concentrations in men. Br J Nutr. 2006 Aug;96(2):357-64

July 2005 – Metabolism **Clinical**

The present study showed that short-term cranberry juice supplementation is associated with significant increase in plasma antioxidant capacity and reduction in circulating OxLDL concentrations. Given the key role that Low-density lipoprotein (LDL) oxidation plays in the development of atherosclerotic cardiovascular disease, the potential of cranberries to reduce LDL susceptibility to oxidation could be of importance in CVD prevention.

Ruel G, Pomerleau S, Couture P, Lamarche B, Couillard C. Changes in plasma antioxidant capacity and oxidized low-density lipoprotein levels in men after short-term cranberry juice consumption. Metabolism. 2005 Jul;54(7):856-61.

Additional Research References

Schell J, Betts NM, Foster M, Scofield RH, Basu A. Cranberries improve postprandial glucose excursions in type 2 diabetes. Food Funct. 2017 Sep 20; 8(9):3083-3090.

Kim MJ, Kim JH, Kwak HK. Antioxidant effects of cranberry powder in lipopolysaccharide treated hypercholesterolemic rats. Prev Nutr Food Sci. 2014 Jun;19(2):75-81.

Labonté K, Couillard C, Motard-Bélanger A, Paradis M-E, Couture P, Lamarche B. Acute effects of polyphenols from cranberries and grape seeds on endothelial function and performance in elite athletes. Sports 2013,1(3):55-68.

Yung LM, Tian XY, Wong WT, Leung FP, Yung LH, Chen ZY, Lau CW, Vanhoutte PM, Yao X, Huang Y. Chronic cranberry juice consumption restores cholesterol profiles and improves endothelial function in ovariectomized rats. Eur J Nutr. 2013 Apr;52(3):1145-55.

Kim MJ, Chung JY, Kim JH, Kwak HK. Effects of cranberry powder on biomarkers of oxidative stress and glucose control in db/db mice. Nutr Res Pract. 2013 Dec;7(6):430-8.

Basu A, Lyons TJ. Strawberries, blueberries, and cranberries in the metabolic syndrome: clinical perspectives. J Agric Food Chem. 2012 Jun 13;60(23):5687-92.

Basu A, Rhone M, Lyons TJ. Berries: emerging impact on cardiovascular health. Nutr Rev. 2010 Mar;68(3):168-77.

Heiss, C., Keen, C. L. & Kelm, M. (2010) Flavanols and cardiovascular disease prevention. Eur Heart J 31: 2583–2592.

Kim, M. J., Jung, H. N., Kim, K. N. & Kwak, H. K. (2008) Effects of cranberry powder on serum lipid profiles and biomarkers of oxidative stress in rats fed an atherogenic diet. Nutr Res Pract 2: 158–164.

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Vita, J. A. (2005) Polyphenols and cardiovascular disease: effects on endothelial and platelet function. Am J Clin Nutr 81: 292S–297S.

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Fuhrman, B. & Aviram, M. (2001) Flavonoids protect LDL from oxidation and attenuate atherosclerosis. Curr Opin Lipidol 12: 41–48.

Porter, M. L., Krueger, C. G., Wiebe, D. A., Cunningham, D. G. & Reed, J. D. (2001) Cranberry proanthocyanidins associate with low-density lipoprotein and inhibit *in vitro* Cu^{2+}-induced oxidation. J Sci Food Agric 81: 1306–1313.

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Wilson, T., Porcari, J. P. & Maher, M. A. (2000) Cranberry juice inhibits metal and non-metal initiated oxidation of human low density lipoproteins in vitro. J Dietary Supplements 2: 5–14.

Wilson, T., Porcari, J. P. & Harbin, D. (1998) Cranberry extract inhibits low density lipoprotein oxidation. Life Sci 62: L381–L386.

ORAL HEALTH

Oral health studies were conducted with cranberry extracts, powders, and juice products.

June 2018 – Nutrition Research **Clinical**

In this two-arm randomized controlled study, a cranberry functional beverage consumed for eight weeks showed improvement in gingival health and bleeding and reduced number of S. mutans. There was no increased risk of caries development.

Woźniewicz, M., et al. (2018). "Consumption of cranberry functional beverage reduces gingival index and plaque index in patients with gingivitis." Nutrition Research 58: 36-45.

December 2017 – Journal of the American College of Nutrition **Clinical**

Consumption of cranberry juice enriched with omega-3 can be beneficial as adjuvant therapy with nonsurgical periodontal therapy in decreasing glycated hemoglobin, increasing HDL-C, and improving periodontal status in patients with diabetes with periodontal disease.

Zare Javid, A., et al. (2018). "Impact of Cranberry Juice Enriched with Omega-3 Fatty Acids Adjunct with Nonsurgical Periodontal Treatment on Metabolic Control and Periodontal Status in Type 2 Patients with Diabetes with Periodontal Disease." J Am Coll Nutr 37(1): 71-79.

April 2017 – Food and Function **In vitro**

An extract prepared from cranberry juice by dialysis known as nondialyzable material (NDM) has been fractionated and each fraction was tested to identify the anti-adhesive constituents. One fraction containing A-type proanthocyanidin oligomers (PACs) and as quercetin derivatives inhibited adhesion-linked activities by oral bacteria.

Neto, C. C., et al. (2017). "Characterization of non-dialyzable constituents from cranberry juice that inhibit adhesion, co-aggregation and biofilm formation by oral bacteria." Food and Function 8(5): 1955-1965.

December 2015 – Public Library of Science One **In vitro**

Cranberry flavonoids, such as A-type proanthocyanidins (PACs) and myricetin, have been shown to inhibit the activity of Gtfs and EPS-mediated bacterial adhesion. Cranberry flavonoids disrupt exopolysaccharides

accumulation and S. mutans survival using a mixed-species biofilm model under cariogenic conditions. Cranberry flavonoids are also shown have an impact on mechanical stability and the in situ pH at the biofilm-apatite interference

Kim, D., et al. (2015). "Cranberry Flavonoids Modulate Cariogenic Properties of Mixed-Species Biofilm through Exopolysaccharides-Matrix Disruption." PLoS One 10(12): e0145844.

June 2015 – Journal of Clinical Periodontology **Clinical**

This double-blind randomized controlled prospective clinical trial showed a decrease in gingival bleeding with use of a nutritional supplement made of oligomeric proanthocyanidins.

Díaz Sánchez, R. M., et al. (2015). "A Prospective, Double-Blind, Randomized, Controlled Clinical Trial in the Gingivitis Prevention with an Oligomeric Proanthocyanidins Nutritional." Journal of Clinical Periodontology 42: 48.

April 2015 – Journal of the Indian Society of Pedodontics and Preventive Dentistry **Clinical**

Children using mouthwash containing high-molecular-weight component of cranberry showed a significant reduction in Streptococcus mutans counts in plaque and saliva compared to the control group that used a placebo mouthwash.

Gupta A, Bansal K, Marwaha M. Effect of high-molecular-weight component of Cranberry on plaque and salivary Streptococcus mutans counts in children: an in vivo study. J Indian Soc Pedod Prev Dent. 2015 Apr-Jun;33(2):128-33.

January 2015 – Contemporary Clinical Dentistry **Clinical**

This double-blind, randomized parallel group clinical trial showed that Cranberry mouthwash is equally effective as Chlorhexidine mouthwash, which is the gold standard against oral infections and could be used as an alternative to the later.

Khairnar MR, Karibasappa GN, Dodamani AS, Vishwakarma P, Naik RG, Deshmukh MA.Comparative assessment of Cranberry and Chlorhexidine mouthwash on streptococcal colonization among dental students: A randomized parallel clinical trial. Contemp Clin Dent. 2015 Jan-Mar;6(1):35-9.

June 2015 – Archives of Oral Biology **In vitro**

Natural polyphenols from cranberry and green tea acted in synergy with the human antimicrobial peptide cathelicidin to reduce the secretion of several cytokines by an LPS-stimulated 3D co-culture model of oral mucosal cells, showing promising results as potential adjunctive therapy for treating inflammatory periodontitis.

Lombardo Bedran TB, Palomari Spolidorio D, Grenier D. Green tea polyphenol epigallocatechin-3-gallate and cranberry proanthocyanidins act in synergy with cathelicidin (LL-37) to reduce the LPS-induced inflammatory response in a three-dimensional co-culture model of gingival epithelial cells and fibroblasts. Arch Oral Biol. 2015 Jun;60(6):845-53.

August 2014 – Journal of Periodontal Research **In vitro**

Cranberry high molecular weight non-dialyzable material, derived from cranberry juice and high in PACs was able to inhibit IL-1β stimulated NF-κB and AP-1 activation as well as the production of IL-6 in human gingival epithelial cells.

Tipton DA, Carter TB, Dabbous MKh. Inhibition of interleukin 1β-stimulated interleukin-6 production by cranberry components in human gingival epithelial cells: effects on nuclear factor κB and activator protein 1 activation pathways. J Periodontal Res. 2014 Aug;49(4):437-47.

April 2014 – Pathogens and Disease **In vitro**

Cranberry extract displayed a significant anti-adhesion activity against Candida spp. when used at low concentrations. In addition, the pretreatment of surfaces with this extract induced an anti-adhesion activity mainly

against C. glabrata yeasts and an antibiofilm activity against C. albicans. This activity was dependent on concentration, species, and strain.

Girardot M, Guerineau A, Boudesocque L, Costa D, Bazinet L,Enguehard-Gueiffier C, Imbert C. Promising results of cranberry in the prevention of oral Candida biofilms. Pathog Dis. 2014 Apr;70(3):432-9

March 2014 – Journal of Indian Society of Periodontology **Review**

An extensive search was carried out in the PubMed database using the terms "cranberry polyphenols" and "periodontitis" together. The institute library was also thoroughly scrutinized for all relevant information. The aim of this paper was to review on the potential role of high molecular weight cranberry fraction on oral tissues and periodontal diseases.

Mukherjee M, Bandyopadhyay P, Kundu D. Exploring the role of cranberry polyphenols in periodontits: A brief review. J Indian Soc Periodontol. 2014 Mar;18(2):136-9.

August 2013 – Journal of periodontal research **In vitro**

Non-dialyzable material (NDM) derived from cranberry juice inhibited lipopolysaccharide-stimulated p65 and constitutive or lipopolysaccharide-stimulated MMP-3 suggestijng that cranberry components may regulate aggressive periodontitis fibroblast inflammatory responses.

Tipton DA, Babu JP, Dabbous MKh. Effects of cranberry components on human aggressive periodontitis gingival fibroblasts. J Periodontal Res. 2013 Aug;48(4):433-42.

July 2013 – The Journal of Periodontology **In vitro/animal**

In vitro, cranberry non-dialyzable material (NDM) inhibited the adhesion of Porphyromonas gingivalis and Fusobacterium nucleatum both onto epithelial cells, TNF-α expression by macrophages and inhibited coaggregation in a dose-dependent manner. NDM consumption by mice attenuated the severity of experimental periodontitis compared with a mixed infection without NDM treatment.

Polak D, Naddaf R, Shapira L, Weiss EI, Houri-Haddad Y. Protective potential of non-dialyzable material fraction of cranberry juice on the virulence of P. gingivalis and F. nucleatum mixed infection. J Periodontol. 2013 Jul;84(7):1019-25.

May 2013 – Biofouling **In vitro**

The effect of PACs on the 3D architecture of biofilms and Streptococcus mutans-transcriptome responses within biofilms was investigated. PACs of DP 4 and particularly DP 8 to 13 were the most effective in disrupting bacterial adhesion to glucan-coated apatitic surface, suggesting that PAC oligomers with a specific DP may be effective in disrupting the assembly of cariogenic biofilms.

Feng G, Klein MI, Gregoire S, Singh AP, Vorsa N, Koo H. The specific degree-of-polymerization of A-type proanthocyanidin oligomers impacts Streptococcus mutans glucan-mediated adhesion and transcriptome responses within biofilms. Biofouling. 2013;29(6):629-40.

October 2012 – Journal of Periodontology **In vitro and In vivo**

NDM from cranberry was found to inhibit the adhesion of both species of bacteria onto epithelial cells, and also inhibit coaggregation in a dose-dependent manner. NDM consumption by mice attenuated the severity of periodontitis when compared with a mixed infection without NDM treatment.

Polak, D., et al. (2012). "The Protective Potential of Non-Dialysable Material Fraction of Cranberry Juice on the Virulence of P. Gingivalis and F. Nucleatum Mixed Infection." Journal of Periodontology.

June 2012 – Journal of agricultural and food chemistry **Review**

In vitro studies have shown that cranberry PACs may be potential therapeutic agents for the prevention and management of periodontitis. This review focusses on the effects of cranberry PACs on connective tissue breakdown and alveolar bone destruction, as well as their potential for controlling periodontal diseases. Authors

conclude that more clinical trials are warranted to better evaluate the potential of these molecules for controlling periodontal diseases.

Feghali K, Feldman M, La VD, Santos J, Grenier D. Cranberry proanthocyanidins: natural weapons against periodontal diseases. J Agric Food Chem. 2012 Jun 13;60(23):5728-35.

April 2012 – Journal of Applied Microbiology **In vitro**

AC-PACs and licochalcone A were found to act in synergy to inhibit P. gingivalis growth and biofilm formation. P. gingivalis adhesion to oral epithelial cells was also inhibited by a combination of the two natural compounds in a synergistic manner. AC-PACs and licochalcone A reduced both MMP-9 and P. gingivalis collagenase activities. AC-PACs and licochalcone A also acted in synergy to reduce the lipopolysaccharide (LPS)-induced secretion of the pro-inflammatory mediators.

Feldman, M. and D. Grenier (2012). "Cranberry proanthocyanidins act in synergy with licochalcone A to reduce Porphyromonas gingivalis growth and virulence properties, and to suppress cytokine secretion by macrophages." Journal of Applied Microbiology 113(2): 438-447.

January 2012 – Journal of biomedicine & biotechnology **In vitro**

In the present study, the effect of low concentrations of NDM on Streptococcus gordonii metabolic activity and biofilm formation on restorative dental surfaces was assessed. NDM selectively inhibited metabolic activity of S. gordonii, without affecting bacterial viability. Inhibiting the metabolic activity of bacteria in biofilm may benefit the health of the oral cavity.

Babu J, Blair C, Jacob S, Itzhak O. Inhibition of Streptococcus gordonii metabolic activity in biofilm by cranberry juice high-molecular-eight component. J Biomed Biotechnol. 2012;2012:590384.

January 2012 – BMC Complementary and Alternative Medicine **In vitro**

Research shows that cranberry Proanthocyanidin type A affects the adherence properties of C. albicans and attenuates the induced inflammatory response. Cranberry PACs also prevent biofilm formation of C. albicans.

Feldman, M., et al. (2012). "Cranberry proanthocyanidins inhibit the adherence properties of Candida albicans and cytokine secretion by oral epithelial cells." BMC Complementary and Alternative Medicine 12: 6.

May 2010 – Journal of the Canadian Dental Association **Review**

Researchers at Laval University in Canada summarize the scientific evidence supporting the potential of cranberry polyphenols to prevent and/or treat dental caries and periodontal disease.

Bonifait L, Grenier D. Cranberry polyphenols: potential benefits for dental caries and periodontal disease. Journal of the Canadian Dental Association 2010; 76: a130.

May 2010 – Antimicrobial Agents and Chemotherapy **In vitro**

The effects of A-type cranberry PACs on the inflammatory response of epithelial cells to Porphyromonas gingivalis were studied.The researchers at Laval University in Canada report the results provide evidence that PACs possess health properties for the treatment of periodontal disease because of their ability to affect the etiology of periodontitis.

La VD, Howell AB, Grenier D. Anti-Porphyromonas gingivalis and anti-inflammatory activities of A-type cranberry proanthocyanidins. Antimicrobial Agents and Chemotherapy 2010; 54:1778-1784.

March 2010 – Caries Research **Animal**

University of Rochester researchers conducted this in vivo study which demonstrates that cranberry PACs reduced the formation of biofilms by Streptococcus mutans and dental caries development, which may be attributed to the presence of specific bioactive A-type dimers and oligomers PACs from cranberry extracts.

Koo H, Duarte S, Murata RM, Scott-Anne K, Gregoire S, Watson GE, Singh AP, Vorsa N. Influence of cranberry proanthocyanidins on formation of biofilms by Streptococcus mutans on saliva-coated apatitic surface and on dental caries development in vivo. Caries Research 2010; 44:116-126.

August 2008 – Critical Reviews in Food Science and Nutrition **Review**

A comprehensive review of the potential oral health benefits of cranberry was published in collaboration with researchers from Laval University in Canada and researchers from Tel-Aviv University in Israel. This research suggests that cranberry components may serve as bioactive molecules for the prevention and/or treatment of oral diseases.

Bodet C, Grenier D, Chandad F, Ofek I, Steinberg D, Weiss EI. Potential oral health benefits of cranberry. Critical Reviews in Food Science and Nutrition 2008; 48:672-680.

December 2007 – *Journal of Periodontal Research*

Researchers at Tokyo Dental College continue to investigate the ability of a cranberry polyphenol fraction to inhibit growth and biofilm formation of *Streptococci mutans* strains.[1] In addition, this group reports that the polyphenol fraction also inhibits biofilm formation and the enzyme activities of *P. gingivalis*.[2] The researchers indicate that results of these studies, taken together with those of earlier studies, suggest that daily use of mouthwashes, toothpaste or chewing gum containing the cranberry polyphenol fraction might prevent the development of dental plaque.

1. Yamanaka-Okada A, Sato E, Kouchi T, Kimizuka R, Kato T, Okuda K. Inhibitory effect of cranberry polyphenol on carcinogenic bacteria. *The Bulletin of Tokyo Dental College* 2008; 49:107-112.

2.Yamanaka A, Kouchi T, Kasai K, Kato T, Ishihara K, Okuda K. Inhibitory effect of cranberry polyphenol on biofilm formation and cystein proteases of Porphyromonas gingivalis. *Journal of Periodontal Research* 2007; 42:589-592.

March 2004 – FEMS Microbiology Letters **Clinical**

A preliminary human study performed at the Hebrew University-Hadassah, Jerusalem, Israel, found that 6 weeks of daily use of a mouthwash supplemented with a cranberry extract led to a significant decrease of certain oral pathogens (Streptococcus mutans) as well as the total bacterial count compared to placebo.

Weiss EI, Kozlovsky A, Steinberg D, Lev-Dor R, Greenstein RBN, Feldman M, Sharon N, Ofek I. A high molecular mass cranberry constituent reduces mutans streptococci level in saliva and inhibits in vitro adhesion to hydroxyapatite. FEMS Microbiology Letters 2004; 232:89-92.

ADDITIONAL RESEARCH REFERENCES

Hrynash H, Pilly VK, Mankovskaia A, Xiong Y, Nogueira Filho G, Bresciani E, Lévesque CM, Prakki A. Anthocyanin incorporated dental copolymer: bacterial growth inhibition, mechanical properties, and compound release rates and stability by (1)h NMR. Int J Dent. 2014:289401.

Plundrich NJ, Kulis M, White BL, Grace MH, Guo R, Burks AW, Davis JP, Lila MA. J Agric Food Chem. Novel strategy to create hypoallergenic peanut protein-polyphenol edible matrices for oral immunotherapy. 2014 Jul 23;62(29):7010-21.

Duarte S, Gregoire S, Singh AP, Vorsa N, Schaich K, Bowen W, Koo H. Inhibitory effects of cranberry polyphenols on formation and acidogenicity of Streptococcus mutans biofilms. FEMS Microbiology Letters 2006; 257:50-56.

Feldman M, Weiss E, Shemesh M, Ofek I, Bachrach G, Rozen R, Steinberg D. Cranberry constituents affect fructosyltransferase expression in Streptococcus mutans. Alternative Therapies in Health & Medicine 2009; 15:32-38.

Gregoire S, Singh AP, Vorsa N, Koo H. Influence of cranberry phenolics on glucan synthesis by glucosyltransferases and Streptococcus mutans acidogenicity. Journal of Applied Microbiology 2007;103:1960-1968.

Koo H, Nino de Guzman P, Schobel BD, Vacca Smith AVV, Bowen WH. Influence of cranberry juice on glucan-mediated processes involved in Streptococcus mutans biofilm development. Caries Research 2006; 40:20-27.

La VD, Howell AB, Grenier D. Cranberry proanthocyanidins inhibit MMP production and activity. Journal of Dental Research 2010; 88:627-632.

Labrecque J, Bodet C, Chandad F, Grenier D. Effects of a high-molecular-weight cranberry fraction on growth, biofilm formation and adherence of Porphyromonas gingivalis. Journal of Antimicrobial Chemotherapy 2006; 58:439-43.

Yamanaka A, Kimizuka R, Kato T, Okuda K. Inhibitory effects of cranberry juice on attachment of oral streptococci and biofilm formation. Journal of Oral Microbiology and Immunology 2004; 19:150-154.

Rajeshwari, H., et al. (2017). "Formulation of thermoreversible gel of cranberry juice concentrate: Evaluation, biocompatibility studies and its antimicrobial activity against periodontal pathogens." Materials Science and Engineering: C **75**: 1506-1514.

La, V. D., et al. (2010). "Anti-Porphyromonas gingivalis and Anti-inflammatory Activities of A-Type Cranberry Proanthocyanidins." Antimicrobial Agents and Chemotherapy 54(5): 1778-1784.

Bodet, C., et al. (2007). "Inhibition of host extracellular matrix destructive enzyme production and activity by a high-molecular-weight cranberry fraction." J Periodontal Res 42(2): 159-168.

CRANBERRY POLYPHENOLS and OTHER BIOACTIVE COMPOUNDS

Content and Measurement

USDA Database for the Proanthocyanidin and Flavonoid Content of Selected Foods

Cranberries were reported to have the highest concentration of total PACs per gram compared to other fruits studied. Cranberries have 418.8 mg/100g followed by wild blueberry (331.9), plum (215.9), cultivated blueberry (179.8) and strawberry (145.0).[1] In addition to the high content of PACs, other flavonoids are abundant in cranberries as well. Quercetin, an important anti-inflammatory molecule is surprisingly high in cranberries (14.84 mg/100 g) compared to foods recommended for its intake including onions (21.40 mg/100g) and broccoli (3.26 mg/100g) and in other commonly consumed fruits, blueberries (7.7 mg/100g), concord grapes (2.08 mg/100g) and apples (3.86 mg/100g). Cranberries have high content of total flavonoids compared to other commonly consumed fruits as well; 114 mg/100 g compared to orange (43.5 mg/100g), concord grapes (73.14 mg/100g), and apples (20 mg/100g).[2]

[1]U.S. Department of Agriculture, Agricultural Research Service. USDA Database for the Proanthocyanidin Content of Selected Foods 2004.

[2]Bhagwat SA, Haytowitz DB, Holden JM. USDA Database for the Flavonoid Content of Selected Foods, Release 3.0, 2011. US Department of Agriculture, Agricultural Research Service Nutrient Data Laboratory Home Page: http://wwwarsusdagov/Services/docshtm?docid=6231.

February 2016- Journal of Agricultural and Food Chemistry

This study reports differential absorbance responses of individual PACs with DMAC. The PAC-DMAC molar absorption coefficients are affected by both DMAC reagent environment and PAC structural variation. Cranberry (A-type) and cocoa (B-type) oligomeric PACs exhibited differential absorbance relationship with degree-of-polymerization. Thus, PAC structural variations have considerable impact on the resulting molar absorption coefficients. The use of DMAC assay in PAC quantification, especially in comparing across specific oligomers and compositions, should not assume molar absorption coefficients are similar.

Wang Y, Singh AP, Hurst WJ, Glinski JA, Koo H, Vorsa N, Influence of Degree-of-Polymerization and Linkage on the Quantification of Proanthocyanidins using 4‑Dimethylaminocinnamaldehyde (DMAC) Assay. J. Agric. Food Chem, 2016, DOI: 10.1021/acs.jafc.5b05408.

January 2016 – Journal of Functional Foods

A extraction method was developed to generate a cranberry PACs standard from whole berries with a high purity >99%. The use of this cranberry PACs standard resulted in values that were 3.6 times higher than those determined by procyanidin A2.[1] The same research group previously found that the use of the cranberry PACs standard from cranberry presscake resulted in higher values of PACs than those determined by A2 and catechin.[2] Researchers suggest that the adoption of cranberry PACs standard should be considered as an improvement over the use of procyanidin A2 for accurate quantification of cranberry PACs.

1. Krueger CG, Chesmore N, Chen X, Parker J, Khoo C, Marais JP Shanmuganayagam D, Crump P, Reed JD. Critical reevaluation of the 4-(dimethylamino)cinnamaldehyde assay: Cranberry proanthocyanidin standard is superior to procyanidin A2 dimer for accurate quantification of proanthocyanidins in cranberry products. Journal of Functional Foods, 2016, 22:13–19.

2. Feliciano RP, Shea MP, Shanmuganayagam D, Krueger CG, Howell AB, Reed JD. Comparison of Isolated Cranberry (Vaccinium macrocarpon Ait.) Proanthocyanidins to Catechin and Procyanidins A2 and B2 for Use as Standards in the 4-(Dimethylamino)cinnamaldehyde Assay. Journal of Agriculture and Food Chemistry, 2012, 60 (18), 4578–4585.

April 2015- The Journal of Nutrition

In this study, a nationally representative database was created to find that the mean intake of flavonoids in U.S. adults aged ≥20 y was 251 mg/d, with flavan-3-ols accounting for 81% of intake. Non-Hispanic whites had significantly higher intakes of total flavonoids than non-Hispanic blacks and Hispanics. The total Healthy Eating Index score increased across flavonoid intake quartiles. Findings suggest that diet quality is positively associated with flavonoid intake.

Sebastian RS, Enns CW, Goldman JD, Martin CL, Steinfeldt LC, Murayi T, Moshfegh AJ. A New Database Facilitates Characterization of Flavonoid Intake, Sources, and Positive Associations with Diet Quality among US Adults. The Journal of Nutrition, 2015, 145:1239–48.

February 2014 – Journal of the Science of Food and Agriculture

Researchers at University of Massachusetts found that PACs had similar oligomer profiles among eight cultivars that sampled from four regions during the 2010 season. Several traditional and newer cultivars of cranberry from various growing regions in North America are excellent sources of PACs, particularly the Howes, Mullica Queen and Early Black cultivars.

Jessica L, Carpenter JL, Caruso FL, Tata A, Vorsac N, Netoa CC. Variation in proanthocyanidin content and composition among commonly grown North American cranberry cultivars (Vaccinium macrocarpon). Journal of Science of Food and Agriculture, 2014, 94(13):2738-45.

May 2013 - Analytical and Bioanalytical Chemistry

Researchers reviewed the qualitative and quantitative analysis of cranberry PACs and states that the structural heterogeneity of “A-type” PACs makes accurate quantification a difficult undertaking. However, as a result of recent advances in MALDI-TOF mass spectrometry, and the cranberry PCAs standard, the integrity of cranberry products can now be determined.

Krueger CG, Reed JD, Feliciano RP, Howell AB. Quantifying and characterizing proanthocyanidins in cranberries in relation to urinary tract health. Analytical and Bioanalytical Chemistry, 2013, 405(13):4385-95

January 2011 - The Journal of Nutrition

U.S. adults over 19 y had a total PACs intake of 95 mg/d, in the order of polymers, monomers, dimers, 4–6 mers, 7–10 mers and trimers. When adjusted for energy intake, the total PACs intake increased with age, was higher in women than men and in alcohol consumers compared with nonconsumers, and was lower in non-Hispanic blacks compared with other ethnicities.

Wang Y, Chung S, Song WO, Chun OK. Estimation of Daily Proanthocyanidin Intake and Major Food Sources in the U.S. Diet. The Journal of Nutrition, 2011, 141: 447–452.

Bioavailability and Bioactivity

November 2018-Natural Product Reports Review

In this review, the role and prospects of phenyl-γ-valerolactones (PVLs) and their related phenylvaleric acids (PVAs) as key metabolites in the understanding of the health features of flavan-3-ols have been critically assessed. Among the topics covered are proposals for a standardized nomenclature for PVLs and PVAs. The formation, bioavailability, and pharmacokinetics of PVLs and PVAs from different types of flavan-3-ols are discussed, taking into account in vitro and animal studies, as well as inter-individual differences and the existence of putative flavan-3-ol metabotypes. Synthetic strategies used for the preparation of PVLs are considered and the methodologies for their identification and quantification assessed. Metabolomic approaches unravelling the role of PVLs and PVAs as biomarkers of intake are also described. Finally, the biological activity of these microbial catabolites in different

experimental models is summarized. Knowledge gaps and future research are considered in this key area of dietary (poly)phenol research.

Mena P, Bresciani L, Brindani N, Ludwig IA, Pereira-Caro G, Angelino D, Llorach R, Calani L, Brighenti F, Clifford MN, Gill CIR, Crozier A, Curti C, Del Rio D. Phenyl-γ-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: synthesis, analysis, bioavailability, and bioactivity. Nat Prod Rep. 2018 Nov 23. doi: 10.1039/c8np00062j.

March 2017-Nutrients **Human study**

Researchers conducted an acute double-blind randomized controlled trial in 10 healthy men with cranberry juices containing 409, 787, 1238, 1534 and 1910 mg total (poly)phenols. Sixty metabolites were identified in plasma and urine including cinnamic acids, dihydrocinnamic, flavonols, benzoic acids, phenylacetic acids, benzaldehydes, valerolactones, hippuric acids, catechols, and pyrogallols. Total plasma, but not excreted urinary (poly)phenol metabolites, exhibited a linear dose response ($r^2 = 0.74$, $p < 0.05$), driven by caffeic acid 4-O-ß-d-glucuronide, quercetin-3-O-ß-d-glucuronide, ferulic acid 4-O-ß-d-glucuronide, 2,5-dihydroxybenzoic acid, 2,4-dihydroxybenzoic acid, ferulic acid, caffeic acid 3-O-ß-d-glucuronide, sinapic acid, ferulic acid 4-O-sulfate, 3-hydroxybenzoic acid, syringic acid, vanillic acid-4-O-sulfate, (4R)-5-(3'-hydroxyphenyl)-γ-valerolactone-4'-O-sulfate, 4-methylgallic acid-3-O-sulfate, and isoferulic acid 3-O-sulfate (all $r^2 \geq 0.89$, $p < 0.05$). Inter-individual variability of the plasma metabolite concentration was broad and dependent on the metabolite. They showed that specific plasma (poly)phenol metabolites are linearly related to the amount of (poly)phenols consumed in cranberry juice.

Feliciano RP, Mills CE, Istas G, Heiss C, Rodriguez-Mateos A. Absorption, Metabolism and Excretion of Cranberry (Poly)phenols in Humans: A Dose Response Study and Assessment of Inter-Individual Variability. Nutrients. 2017 Mar 11;9(3). pii: E268. doi: 10.3390/nu9030268.

January 2016 - Archives of Biochemistry and Biophysics **Human study**

Researchers detected a total of 60 cranberry-derived phenolic metabolites after cranberry juice consumption using UHPLC-Q-TOF-MS. The most abundant plasma metabolites after cranberry juice consumption were small phenolic compounds. This extensive study of cranberry polyphenols bioavailability lays important groundwork necessary to start understanding the fate of these compounds in humans.

Feliciano RP, Boeres A, Luca Massacessi A, Istas G, Ventura MR, Santos C, Christian Heiss C, Rodriguez-Mateos A, Identification and quantification of novel cranberry-derived plasma and urinary (poly)phenols. Archives of Biochemistry and Biophysics, 2016, doi: 10.1016/j.abb.2016.01.014.

June 2015 – Journal of Agricultural and Food Chemistry **In Vitro/Cell Culture**

Cranberry juice consumption has long been recognized for the prevention of urinary tract infections. One mechanism by which cranberry may prevent UTIs is through an anti-adhesion activity of proanthocyanidins against p-fimbriaed Escherichia coli. In this study, researchers from the USDA demonstrated that cranberry xyloglucan oligosaccharide fractions inhibited the adhesion of E. coli to bladder epithelial cells, representing a new cranberry bioactive component with E. coli anti-adhesion activity and high affinity for type 1 fimbriae.

Hotchkiss AT, Nunez A, Strahan GD, Chau H, White A, Marais J, Hom K, Vakkalanka MS, Di R, Yam KL, Khoo C. Cranberry Xyloglucan Structure and Inhibition of Escherichia coli Adhesion to Epithelial Cells. J Agric Food Chem. 2015 Jun 17;63(23):5622-33

May 2015 – Journal of Functional Foods

The research group in University of Rhode Island extracted a phenolic-free, oligosaccharide component from cranberry fruit and characterized is as mainly xyloglucan and arabinan residue. Researchers found that this oligosaccharide component reduced biofilm production by both uropathogenic and non-pathogenic *Escherichia coli*. The researchers state that the results suggested that in addition to PACs and other polyphenols, certain carbohydrate components in cranberry may play a role in its preventive effects against urinary tract infections.

Sun J, Marais JP, Khoo C, LaPlante K, Vejborg RM, Givskov M, Tolker-Nielsen T, Seeram NP, Rowley DC. Cranberry (*Vaccinium macrocarpon*) oligosaccharides decrease biofilm formation by uropathogenic *Escherichia coli.* Journal of Functional Foods, 2015, 17, 235–242.

May 2015 – International Journal of Molecular Science **In Vitro /Cell Culture**

Researchers at the Institute of Food Science Research in Madrid investigated the effects of cranberry phenolic compounds and their potential microbial-derived metabolites were tested for their capacity to inhibit the adherence of uropathogenic Escherichia coli to bladder cells. Catechol, benzoic acid, vanillic acid, phenylacetic acid and 3,4-dihydroxyphenylacetic acid showed anti-adhesive activity against UPEC in a concentration-dependent manner, and were more effective than procyanidin A2. These results demonstrate for the first time that the anti-adhesive activity of some cranberry-derived phenolic metabolites against E.coli in vitro, suggesting that their presence in the urine could reduce bacterial colonization and progression of UTI.

de Llano DG, Esteban-Fernández A, Sánchez-Patán F, Martínlvarez PJ, Moreno-Arribas MV, Bartolomé B. Anti-Adhesive Activity of Cranberry Phenolic Compounds and Their Microbial-Derived Metabolites against Uropathogenic Escherichia coli in Bladder Epithelial Cell Cultures. Int J Mol Sci. 2015 May 27;16(6):12119-30.

February 2015 –Journal of Functional Foods

Researchers at the University of Florida investigated the overall metabolome changes caused by cranberry juice using a global ^{1}H NMR-based metabolomics approach. The study demonstrates that overall metabolites profiles after drinking cranberry juice were different from those following apple juices. Cranberry juice caused a greater increase in hippuric acid, citric acid, and a decrease in lactate, D-glucose compared to apple juice consumption.

Liu H, Tayyari F, Khoo C, Gu L, A ^{1}H NMR-based approach to investigate metabolomic differences in the plasma and urine of young women after cranberry juice or apple juice consumption. Journal of Functional Foods, 2015, 14: 76-86.

November 2014 – Nutrition Research

Using nationally representative dietary data for U.S. adults ≥19 years, researchers found that consumption of cranberry juice cocktail is associated with healthier anthropometric and inflammatory profiles compared with non-consumption. Adult cranberry juice cocktail consumers had significantly lower levels of C-reactive protein. Despite the addition of sugar, researches did not find that cranberry juice cocktail consumption was associated with higher weight or an increased likelihood for overweight or obesity, nor did consumers have higher total energy intake compared with non-consumers.

Duffey KJ, Sutherland LA. Adult consumers of cranberry juice cocktail have lower C-reactive protein levels compared with nonconsumers. Nutrition Research, 2015, 35 (2): 118–126.

July 2014 -Food Chemistry

Researchers found that phenolic acids and flavonoids in cranberry juice cocktail are bioavailable and increase antioxidant capacity in healthy older adults following a low-calorie cranberry juice cocktail. The type-A procyanidin dimer (A2) is detected in plasma and quantified in urine following an acute does of cranberry juice cocktail.

McKay DL, Chen CY, Zampariello CA, Blumberg JB. Flavonoids and phenolic acids from cranberry juice are bioavailable and bioactive in healthy older adults. Food Chemistry, 2015, 168: 233–240

June 2014 – Food Chemistry

Researchers developed two processes to depolymerize the polymeric PACs in cranberries into oligomers, which were transported through Caco-2 cell monolayers. The study provided an effective method to convert un-bioavailable PAC polymers to bioavailable oligomers[1]. Ou and colleagues previously reported that A-type PAC dimers, trimers and tetramers from cranberry can be absorbed across Caco-2 cells. The results suggested that A-type PAC dimers, trimers, and tetramers are bioavailable in humans after cranberry consumption[2].

1. Ou K, G L. Depolymerisation optimisation of cranberry procyanidins and transport of resultant oligomers on monolayers of human intestinal epithelial Caco-2 cells. Food Chemistry, 2015, 167: 45–51.

2. Ou K, Percival S, Zou T, Khoo C, Gu L. Transport of Cranberry A-Type Procyanidin Dimers, Trimers, and Tetramers across Monolayers of Human Intestinal Epithelial Caco-2 Cells J. Agric.Food Chem, 2012, 60:1390−1396.

February 2013 - Food and Chemical Toxicology

Researchers developed a rapid and sensitive analytical technique to identify a total of 32 metabolites including phase I and phase II metabolites. Among them, free phenolic acid derivatives, flavonols and one coumarin were detected in the human urine.

Iswaldi I, David Arráez-Román D, Gómez-Caravaca AM, Contreras MM, Uberos J, Segura-Carretero A, Fernández-Gutiérrez A. Identification of polyphenols and their metabolites in human urine after cranberry-syrup consumption, Food and Chemical Toxicology, 2013, 55: 484–492.

December 2013 – Nutrients

A significantly higher proportion of cranberry beverages consumers were predicted to be normal weight and had to have lower waist circumferences in U.S. adults ≥19 y. The low and middle level cranberry beverages consumers compared to non-consumers were more likely to be normal weight and less likely to be overweight/obese. Findings of this study suggest that there may be a role for consumption of cranberry juice beverages as part of a healthy diet and lifestyle, despite the fact that they are sweetened with nutritive sweeteners.

Duffey KJ, Sutherland LA, Adult Cranberry Beverage Consumers Have Healthier Macronutrient Intakes and Measures of Body Composition Compared to Non-Consumers: National Health and Nutrition Examination Survey (NHANES) 2005–2008. Nutrients, 2013, 5, 4938-4949.

April 2010 – Journal of Nutrition

This pilot study conducted at Tufts University was undertaken in 15 participants with coronary artery disease to determine the pharmacokinetics of cranberry anthocyanidins. The researchers state the findings of this study suggest that anthocyanin concentrations are too low to directly contribute to in vivo quenching of reactive oxygen species but may be adequate to influence signal transduction and gene expression pathways.

Milbury PE, Vita JA, Blumberg JB. Anthocyanins are bioavailable in humans following an acute dose of cranberry juice. Journal of Nutrition 2010 Jun;140(6):1099-104.

March 2009 – Journal of Medicinal Food In vitro/Cell Culture

In an earlier publication, researchers from Worcester Polytechnic Institute describe the ability of cranberry PACs to alter the shape of certain E. coli bacteria that cause UTI, and propose this effect as one way cranberry PACs can disable bacteria. Continuing on this previous research, Camesano and colleagues investigate the ability of cranberry PACs to decrease the adhesion forces as the mechanism for disabling these bacteria and confirm the mechanism of action is associated with an interference of bacterial attachment to uroepithelial cells by modification of surface properties of bacteria.

Pinzon-Arango PA, Liu Y, Camesano T. Role of cranberry on bacterial adhesion forces and implications for Escherichia coli-uroepithelial cell attachment. Journal of Medicinal Food 2009; 12:259-270.

July 2008 – Journal of Agriculture and Food Chemistry

The quantities of polyphenols in cranberry products were evaluated by a research group at the University of Scranton in Pennsylvania. The results demonstrate cranberries to be an excellent source of antioxidants.[1] Vinson and colleagues previously reported that on a fresh weight basis, cranberry was reported to have the highest concentration of polyphenols of 20 fruits tested. Cranberry powder was also a potent inhibitor of LDL oxidation, suggesting a cardioprotective effect of its antioxidant activity.[2]

1. Vinson JA, Bose P, Proch J, Al Kharrat H, Samman N. Cranberries and cranberry products: powerful in vitro, ex vivo, and in vivo sources of antioxidants. Journal of Agriculture and Food Chemistry 2008; 56:5884-5891.

2. Vinson JA, Su X, Zubik L, Bose P. Phenol antioxidant quantity and quality in foods: fruits. Journal of Agriculture and Food Chemistry 2001; 49:5315-5321.

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Ou K, Sarnoski P, Schneider KR, Song K, Khoo C, Gu L. Microbial catabolism of procyanidins by human gut Microbiota. Molecular Nutrition and Food Research, 2014, 58, 2196–2205.

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