NATUREX-DBS, LLC

pacran®

Whole Cranberry Synergies for Urinary Tract Health

Presented by the *Cranberry Ingredient Experts*, May 2013

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Welcome:

Thank you for taking the time to learn more about Pacran®. The aim of this paper is to provide the reader with a thorough understanding of Pacran®'s role in supporting urinary tract health.

We will explore:

- Cranberry's "mechanism of action"
- Key phytochemicals in cranberry
- Current cranberry analytical methods
- The latest generic cranberry clinical science and published literature developed to support cranberry's urinary tract health benefits
- Cranberry's urinary tract health claim status worldwide
- How to define an effective daily dose
- Cranberry intellectual property.

Of course, this paper will provide an in depth analysis of Pacran®. We will discuss the Pacran® formulation, why we chose to formulate as such and all of the independent substantiation that we have built to support Pacran®'s urinary tract health benefits.

Please reach out to your cranberry ingredient experts at NATUREX-DBS if you would like to discuss Pacran® further.

Thank you,

The Cranberry Ingredient Experts

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Pacran®:

All Natural, Whole Cranberry Synergies for Urinary Tract Health

Over 75 Years in the Making

Pacran® was designed and built from the ground up to help support urinary tract health. NATUREX-DBS leveraged our expertise in cranberries to design the most effective Urinary Tract Health cranberry ingredient in the world. We selected naturally superior raw materials such as Early Black cranberries, identified the key active ingredients for standardization and optimized the manufacturing processes to assure high quality, reproducible finished goods. From there we selected the finest methods of analysis, conducted safety and gold standard human clinical efficacy studies and eventually applied for and received a government sanctioned health claim.

Harnessing the Power of the Whole Cranberry

Pacran® is an all-natural, 100% cranberry, whole fruit powder. Pacran® has one ingredient – cranberry – just as nature intended it. Pacran® is made exclusively with North American *Vaccinium macrocarpon* cranberries.

Most competitive cranberry products are derived from cranberry fractions such as juice concentrate or certain isolated phytochemicals such as Proanthocyanidins (PACs), Pacran® is a proprietary blend of the whole fruit. Pacran® offers it all; the juice, the flesh, the skins and the seeds. As a whole cranberry matrix Pacran® delivers the entire spectrum of the cranberry.

Pacran® Cranberry Matrix vs. Cranberry Fractions

Characteristic	Pacran®	Cranberry Extracts	Cranberry Concentrate Powders
Juice	√	√	√
Skins	√		
Flesh	√		
Seed	√		
PACs	√	√	√
Phenolics	√	√	√
Organic Acids	√		√
Fiber	√		
Sugars	√		√
Fatty Acids	√		

Health Claims Status

A single 500 mg dose of Pacran® has the human clinical substantiation necessary to support a "Supports Urinary Tract Health" Structure Function Claim. That same 500 mg dose has been awarded a Health Functional Food claim from the Korean Food and Drug Administration. Pacran® is the first cranberry ingredient in the world that can freely market a government sanctioned health claim.

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Unmatched Intellectual Property

Pacran® is a whole cranberry powder supported by six US and three international patents. As such, customers can be rest assured that their investment in Pacran® is protected by the broadest and most far reaching of all cranberry based patents:

United States Patents:

- 5,474,774 – *Adhesion Inhibiting Composition*
- 5,525,341 – *Partially Purified Cranberry Anti-Adhesion Activity*
- 5,646,178 – *Cranberry Extract and Biologically Active Compounds Derived Therefrom*
- 5,650,432 – *Method of Treating or Preventing Non-Viral Infection*
- 6,608,102 and 6,720,353 – *Plant Proanthocyanidin Extract Effective at Inhibition Adherence of Bacteria with P-Type Fimbriae to Surfaces*

Australian Patents:

- 703158 – *Method of Treating or Preventing Non-viral Microbial Infection*
- 708657 – *Adhesion Inhibiting Composition*

United Kingdom Patent:

- 0752871 –*Adhesion Inhibiting Vaccinium Extract*

Industry Leading Science

Pacran®'s proprietary formulation is standardized and reproducible. Pacran® has been the subject of a many research studies including; published and proprietary human clinical trials, cross-over studies, comparative cross-over studies and published safety studies.

Pacran®, the Whole Package

Pacran® delivers the whole berry synergies that Mother Nature intended. A single compliance friendly, cost effective, 500 mg daily dose has been clinically shown to support urinary tract health with permissible health claims. Clearly, Pacran® delivers on all fronts:

Industry Leading Health Claim Status –	√
Most Cost Effective Efficacious Dose –	√
Unmatched Clinical Substantiation –	√
500 mg Compliance Friendly Dose –	√
Strongest and Broadest IP Protection –	√
Safe, All-Natural and GRAS –	√

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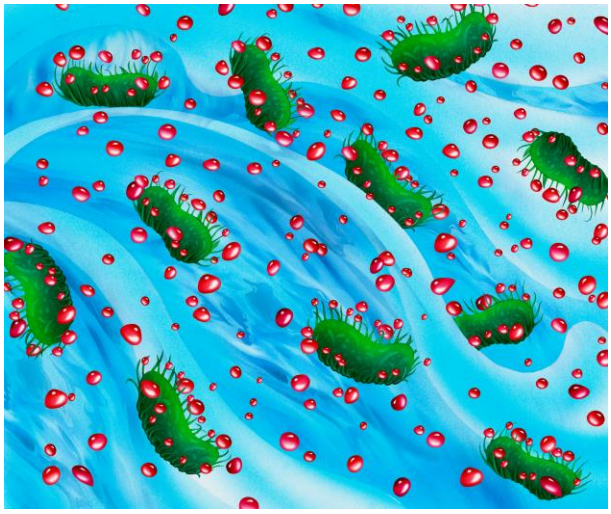
Cranberry's Mechanism of Action:

Natural Anti-Adhesion, the Bugs Don't Stick

Bacterial Anti-Adhesion

E. coli bacteria cause 85-95% of urinary tract infections. In order to support urinary tract health cranberries act upon and mitigate the risk of *E. coli* infection. Since cranberries are naturally rich in a wide variety of phytochemicals including organic acids, early theories regarding the mechanism of action of cranberry involved the acidification of urine. It was thought that cranberries create an acid environment in the urine in which *E. coli* bacteria cannot survive. However, science has shown that the urinary pH is not affected by consumption of cranberry.

For the last two decades, research has focused on and continues to grow in support of cranberry's unique anti-adhesion capabilities. It is widely believed that the unique blend of active phytochemicals found in cranberry provide anti-adhesion activity. *E. coli* bacteria gain entrance to the urinary tract, use their hair-like fimbriae to build a biofilm or protective colony and eventually form an infection. Cranberries inhibit *E. coli* bacterial adhesion to cell walls. By inhibiting adhesion to cell walls the bacteria are unable to form a bioflim and create an infection. Most of the research has focused on a single molecular group, Proanthocyanidins (PACs), as the phytochemical solely responsible for anti-adhesion. However, mounting published research (2011 and 2012) suggests that whole cranberry matrices out perform PAC rich fractions. The synergies of the whole fruit offer more potent anti-adhesion benefits.



Whole Cranberry Matrices vs. Cranberry Fractions

Emerging science is identifying whole cranberry complexes, not cranberry fractions such as PACs, as more effective as supporting urinary tract health. In fact, health claim petitions based on cranberry fractions (cranberry juice or PACs) have been denied by government regulatory bodies such as the European Food Safety Authority (EFSA). EFSA consistently cites a dearth of product specific clinical evidence as the reason for the PAC-based cranberry fraction health claim petition denials. To date all EFSA Article 13.1 and 13.5 cranberry-based urinary tract health petitions have been rejected. What's more a product specific cranberry juice and sweetened and dried cranberries petition was rejected under the EFSA 14.1 framework. These petitions were based on a daily dose of PACs and were denied due to insufficient substantiation. The petitions lacked the clinical evidence necessary to support the requested claim.

Beyond that, three recent (2011 and 2012) gold standard clinical research investigations funded by the National Institutes of Health were unable to generate statistically significant reduction in UTI recurrence rates for cranberry juice (a partial cranberry fraction) vs. placebo. Further, PAC-only cranberry fractions were out performed by cranberry juice / juice powder in two recent studies.

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Recent clinical results on cranberry fractions:

Study	Product Studied	Authors & Journal	Conclusion
Cranberry Juice for the Prevention of Recurrences of Urinary Tract Infections in Children: A Randomized Placebo-Controlled Trial	Cranberry Juice Cocktail	CID 2012:54 (1 February), Salo et al	**"The intervention did not significantly reduce the number of children who experienced a recurrence of UTI…"**
Cranberry Juice Fails to Prevent Recurrent Urinary Tract Infection: Results From a Randomized Placebo-Controlled Trial	Cranberry Juice Cocktail	CID 2011:52 (1 January), Barbosa-Cesnik et al	**"Among otherwise healthy college women with an acute UTI, those drinking 8 oz. of 27% cranberry juice twice daily did not experience a decrease in the 6-month incidence of a second UTI, compared with those drinking a placebo."**
Recurrent Urinary Tract Infection and Urinary *Escherichia coli* in Women Ingesting Cranberry Juice Daily: A Randomized Controlled Trial	Cranberry Juice Cocktail (Splenda)	Mayo Clinic Proceedings February 2012;87(2): 143-150, Stapleton, et al	**"Cranberry juice did not significantly reduce UTI risk compared with placebo…"**
Impact of Cranberry Juice and Proanthocyanidins on the Ability of Escherichia coli to Form Biofilms	Cranberry Juice Cocktail and Cranberry PAC fraction	Food Sci. Biotechnol. 20(5): 1315-1321 (2011), Pinzón-Arango et al	**"Our results suggest that the combination of different active compounds in cranberry juice has a better ability to inhibit the formation of biofilms on PVC substrates than just isolated PACs…"**
Inhibition of Adhesion of Uropathogenic Escherichia coli Bacteria to Uropepithelial Cells by Extracts from Cranberry	Cranberry PAC Fractions (Extract A & C) and Cranberry PAC Fraction + Cranberry Juice Concentrate Powder (Extract B)	Journal of Medicinal Food 15 (2) 2012, 126-134 Ermel, et. al.	"The effects of the different assayed extracts were not obviously different except for extract B, which inhibited approximately 55% of adhesion at an equivalent PAC concentration of 5 µg/ml."

These studies as well as the recent opinions of the European Food Safety Authority (EFSA) suggest that fractions such as Cranberry Juice Cocktail and PAC extracts do not have sufficient substantiation. Meanwhile, as detailed later, the whole cranberry formulation of Pacran® showed statistically significant reduction in UTI recurrence rate vs. placebo control in a recent gold standard clinical trial.

Proanthocyanidins

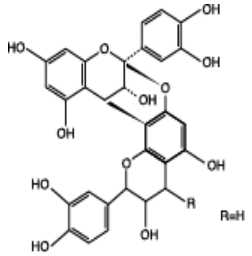
Cranberries Most Popular Fraction

Proanthocyanidins (PACs) are a class of biologically active flavonoids found throughout the plant kingdom and are one of the most potent antioxidants in nature. Typically concentrated in the bark of trees and in the outer shells of fruits and seeds, Proanthocyanidins serve to protect plants against oxidative elements such as oxygen and sunshine.

PACs have been identified as one of the phytochemicals responsible for many of the health benefits associated with cranberries. Cranberries contain unique A-type PACs, seldom found elsewhere in nature. Though many plant sources contain PACs, only the cranberry's unique A-linked PACs exhibit *ex vivo* bacterial anti-adhesion activity. B-link PAC found in many botanicals including; dark chocolate, apples, grapes, etc. do not display bacterial anti-adhesion.

36 mg of PACs

The global fixation on PACs stems from the 2004 AFFSA (France's Food Safety Authority) generic cranberry health claim. This claim put PACs, or more precisely 36 mg of North American Cranberry *Vaccinium macrocarpon* PACs, on the forefront of formulators' minds. The claim provided a generally accepted framework for formulators to deliver an effective dose of cranberry. Prior to the health claim cranberry supplements were typically not standardized to an active ingredient.



Proanthocyanidin

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The petitioners defined 36 mg of PACs as an effective dose based on three pieces of science:

1. Daily consumption of a *10 oz. glass (300 ml) of Cranberry Juice Cocktail (CJC) containing 27% cranberry has been clinically shown to support* urinary tract health.[1]
2. A glass of CJC was shown to have 36 mg of PACs.[2]
3. PACs have been identified as an active ingredient in cranberry providing cranberry's bacterial anti-adhesion activity. Literature has shown bacterial anti-adhesion to be the mechanism of action responsible for cranberry's urinary tract health benefits.[3]

The petitioners argued that the 36 mg of PACs found in a glass of CJC is an effective dose for urinary tract health, and that products containing 36 mg of PACs should have the same urinary tract health benefits as a glass of CJC. Based on this argument AFFSA authorized the following claim for products containing a minimum of 36 mg of North American Cranberry *Vaccinium macrocarpon* PACs:

> *"Cranberry can help reduce the adhesion of certain E. coli bacteria to the urinary tract walls"*

As referenced earlier EFSA has rejected all article 13.1 and 13.5 petitions including the AFFSA claim submission due to lack of substantiation. Thirty-six (36) mg of PACs health claims are no longer permissible.

PAC Method of Analysis (MOA)

There are three generally recognized MOA available for quantifying the content of PACs. Each method has its strengths and weaknesses including; reproducibility, cost, availability of reference standards, turn-around time, etc.

- **HPLC:** The monomeric components are determined by HPLC analysis and are subtracted from the total polyphenol content (determined by reaction with Folin-Ciocalteu Reagent) to yield the oligomeric proanthocyanidin content.

- **BL DMAC:** 4-dimethylaminocinnamaldehyde (DMAC) colorimetric method uses a commercially available standard (procyanidin A2), for the standard method for quantification of proanthocyanidins (PACs) in cranberry powders

- **European Pharmacopeia:** Spectrophotometric assay for the quantification of the proanthocyanidin (PAC) content in cranberry extracts. This method is directly adapted from the European Pharmacopoeia describing PAC assay in hawthorn berries (European Pharmacopoeia 6.0; 01/2008:1220).

Pacran® was developed and standardized using the HPLC method. However, PAC values can be reported using any of the methods listed above.

1"Reduction of Bacteriuria and Pyuria After Ingestion of Cranberry Juice," Jerry Avorn, MD; Mark Monane, MD. MS, Jerry H. Gurwitz, MD; Robert J. Glynn, PhD;
lgor Choodnovskiy; Lewis A. Lipsitz, MD, JAMA, March 9, 1994 - Vol 271, No. 10
2"Analysis and Standardization of Cranberry Products," Cunningham DG, Vannozzi S, O'Shea E, and Turk R. 2002 American Chemical Society p. 151- 166
3"The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-Fimbriated Escherichia coli in vitro," Lai Yeap Fooa,*, Yinrong Lua, Amy B. Howellb, Nicholi Vorsa, Phytochemistry 54 (2000) 173-181

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Cranberry Health Claims:

Product Specific Science Delivers Product Specific Health Claims

The Pacran® Health Claim:

Pacran® is the first cranberry ingredient in the world that can freely market a government sanctioned health claim. The Korean Food and Drug Administration (KFDA) rewards Health / Functional Food claims based on product specific evidence. On November 3rd 2009 Pacran® was awarded Certificate of Health Functional Food Number 2009-84, the claim reads:

> "By reducing bacteria adhesion on urinary tract walls, Pacran® may help to support urinary tract health."

Full details of the KFDA Health / Functional Food process are outlined in *Regulations on health/functional foods in Korea,* Kim, et. al. Toxicology 221 (2006) 112–118

US Structure Function Claims

Structure Function Claims (SFC) are broad-based claims that state that a product can support the structure or function of the body.

The evidence which must be established to substantiate a SFC is the standard of "competent and reliable scientific evidence", which was originally defined by the FTC, and later adopted by the FDA. The standard of competent and reliable scientific evidence is defined as "*tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results".*

In recent litigation cases involving the FTC (plaintiff) and several different defendants (The Dannon Company, Nestle, Beiersdorf, Iovate), the standard of competent and reliable scientific evidence was very specifically defined as consisting of, *"At lease two adequate and well-controlled human clinical studies of the product… conducted by different researchers, independently of each other, that conform to acceptable designs and protocols and whose results, when considered in light of the entire body of relevant and reliable scientific evidence, are sufficient to substantiate that the representation is true".*

Nutritional supplements marketed in the USA and which contain 500 mg of Pacran® have the competent and reliable scientific evidence to support the following Structure Function Claim "Pacran® helps support urinary tract health."

European Claims:

Currently there are no approved cranberry based Urinary Tract Health claims in Europe. All cranberry urinary tract health petitions submitted to EFSA have been denied.

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Pacran® Substantiation

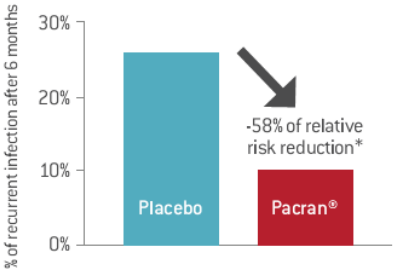
Unmatched Support for a Healthy Urinary Tract

Pacran® had been the subject of a tremendous amount of research and development. Currently, Pacran® boasts two urinary tract health double blind, controlled, human clinical trials, human *ex vivo* cross-over studies and many *ex vivo* comparative cross-over studies.

Pacran®'s Clinical Effect on UTI Recurrence Rates:

"A randomized double blind placebo controlled trial to evaluate the efficacy of cranberry powder as a prophylactic against recurrent urinary tract infection in women" (Vidlar, et. al.)

A 180 day clinical study was conducted to evaluate the effect of 500 mg of Pacran® on the recurrence of symptomatic Urinary Tract Infections (UTI) in women compared to placebo. The daily dose of 500 mg Pacran® reduced UTI recurrence rates by 58% compared to placebo (p>0.05).

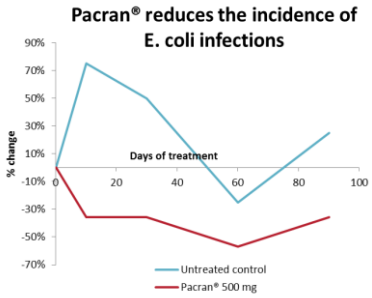


Pacran®'s Clinical Effect on *E. coli*:

"A randomized, double blind, controlled, dose dependent clinical trial to evaluate the efficacy of a proanthocyanidin standardized whole cranberry (Vaccinium macrocarpon) powder on infections of the urinary tract" (Sengupta, et. al.) Current Bioactive Compounds 2011, *7*, 39-46 39

A 90 day clinical study was conducted to determine the effect of Pacran® on bacteriuria and pyuria in women. The data show that a daily dose of 500 mg of Pacran® helps to support a healthy urinary tract system. Results of this study were published in the journal *Current Bioactive Compounds.*

After the 90-day follow up period, there was a 36% reduction of urinary *E. coli* infection reported in the 500 mg/day group. Whereas, change in the presence of *E. coli* at 90 days in the untreated control group was not significant when compared to baseline. Pacran® showed significant reduction in urinary *E. coli* as well as symptoms compared to the control group.



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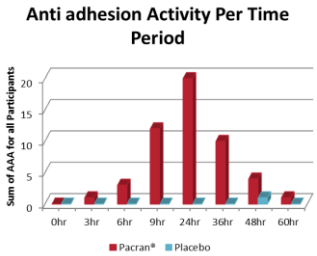
Pacran® *Ex Vivo* Crossover Trial

A randomized, double-blinded, placebo controlled crossover trial was conducted to determine the *ex vivo* uropathogenic bacterial P-type anti-adhesion activity (AAA) in human urine following consumption of either 500-mg Pacran® capsule or a placebo capsule with a 7-day wash-out period, measured over a 60 hour time frame with product consumed at the beginning of the test period only.

"Assessment of bacterial anti-adhesion activity of Pacran® in human urine against P-type uropathogenic Escherichia coli. A randomized, placebo-controlled, ex vivo, double-blind, crossover trial" Amy Howell, Ph.D., Associate Research Scientist, Rutgers University,

Pacran® had higher total AAA than Placebo over all time periods for all participants combined. These results were highly significant ($p<0.0001$). By time period, AAA of Pacran® was significantly higher than Placebo from 9 to 36 hours after ingestion ($p<0.0001$ at 9 and 24 hours, and $p=0.0003$ at 36 hours). Placebo ingestion resulted in no significant AAA at any time period.

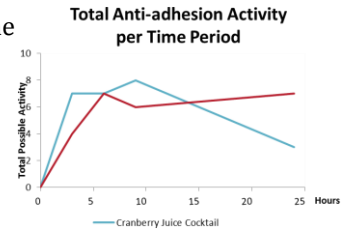


Pacran® *Ex Vivo* Pilot Comparative Studies

Two separate cross-over comparative studies conducted at Rutgers University comparing *ex vivo* bacterial AAA of human urine after consumption of commercially available cranberry fractions are highlighted below. The results show that 500 mg of Pacran® containing just 2 mg of PACs per dose is just as effective at providing the AAA as 300 ml of Cranberry Juice Cocktail (CJC) containing 38 mg of PACs or PAC rich extract containing 33 mg of PACs.

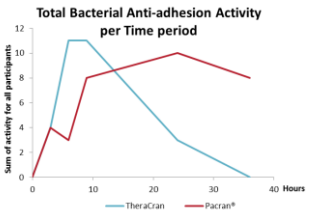
"Bacterial Anti-adhesion Activity of Human Urine Following 27% Cranberry Juice Cocktail vs. Pacran® Capsule Consumption," presented at ACS 2009 Annual Meeting - February 24, 2009 Amy Howell, Ph.D., Associate Research Scientist, Rutgers University.

Summing all observed AAA recorded for all participants over every time period yielded nearly identical results for each product (25 out of a possible 80 for CJC, and 24/80 for Pacran®). By time period, the post-CJC urinary activity increased steadily from 3 to 9 hrs and dropped off significantly at 24 hrs. The post-Pacran® urinary activity increased to a high at 6 hrs, dropped off at 9 hrs and then increased again at 24 hrs.



"Bacterial Anti-adhesion Activity of Human Urine: Pacran® Capsule vs. TheraCran® Capsule Consumption,"* Amy Howell, Ph.D., Associate Research Scientist, Rutgers University, September 23, 2009.

Summing all observed AAA recorded for all participants over every time period yielded 29 out of a possible 120 for TheraCran® and 33/120 for Pacran®. The overall difference between the products was not statistically significant. This suggests that TheraCran® has a more rapid and substantial effect in the first 6 hours, which it maintains at 9 hours, but diminishes thereafter. The Pacran® activity appears to slowly increase over time and reaches peak activity at about 24 hours.



These *ex vivo* data provide further evidence that whole cranberry matrices such as Pacran at 2 mg of PACs deliver synergistic benefits for UT health vs. cranberry fractions at 34-38 mg of PACs.

*TheraCran® is a registered trademark of TheraLogic, LLC

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Pacran®:

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The evidence is clear. Pacran® is the best solution for urinary tract health formulations. The all natural, 100% *Vaccinium macrocarpon* whole cranberry formulation of Pacran® delivers; the science, the health claim, and the intellectual property at a fraction of the cost of the competition.

Contact your cranberry ingredient expert to learn more today.

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References:

1. Reduction of Bacteriuria and Pyuria After Ingestion of Cranberry Juice, Avorn, et. al, JAMA, March 9, 1994 - Vol 271, No. 10

2. Analysis and Standardization of Cranberry Products, Cunningham, et al, 2002 American Chemical Society p. 151- 166

3. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-Fimbriated Escherichia coli in vitro, Foo, et al, Phytochemistry 54 (2000) 173-181

4. Cranberry Juice for the Prevention of Recurrences of Urinary Tract Infections in Children: A Randomized Placebo-Controlled Trial, Salo et al, CID 2012:54 (1 February)

5. Cranberry Juice Fails to Prevent Recurrent Urinary Tract Infection: Results From a Randomized Placebo-Controlled Trial, Barbosa-Cesnik, et al, CID 2011:52 (1 January)

6. Impact of Cranberry Juice and Proanthocyanidins on the Ability of Escherichia coli to Form Biofilms Food Sci. Biotechnol. Pinzón-Arango et al, 20(5): 1315-1321 (2011)

7. Bacterial Anti-adhesion Activity of Human Urine Following 27% Cranberry Juice Cocktail vs. Pacran® Capsule Consumption, Howell, Rutgers University

8. Bacterial Anti-adhesion Activity of Human Urine: Pacran® Capsule vs. TheraCran® Capsule Consumption, Howell, Rutgers University

9. A randomized, double blind, controlled, dose dependent clinical trial to evaluate the efficacy of a proanthocyanidin standardized whole cranberry (Vaccinium macrocarpon) powder on infections of the urinary tract, Sengupta, et al, Current Bioactive Compounds 2011, 7, 39-46 39

10. A randomized double blind placebo controlled trial to evaluate the efficacy of cranberry powder as a prophylactic against recurrent urinary tract infection in women. Vidlar, et al

11. Recurrent Urinary Tract Infection and Urinary *Escherichia coli* in Women Ingesting Cranberry Juice Daily: A Randomized Controlled Trial, Stapleton, et al, Mayo Clinic Proceedings February 2012;87(2): 143-150

12. Bacterial Anti-adhesion Activity of Human Urine: Pacran® Capsule vs. TheraCran®

13. Assessment of bacterial anti-adhesion activity of Pacran® in human urine against P-type uropathogenic Escherichia coli. A randomized, placebo-controlled, ex vivo, double-blind, crossover trial

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