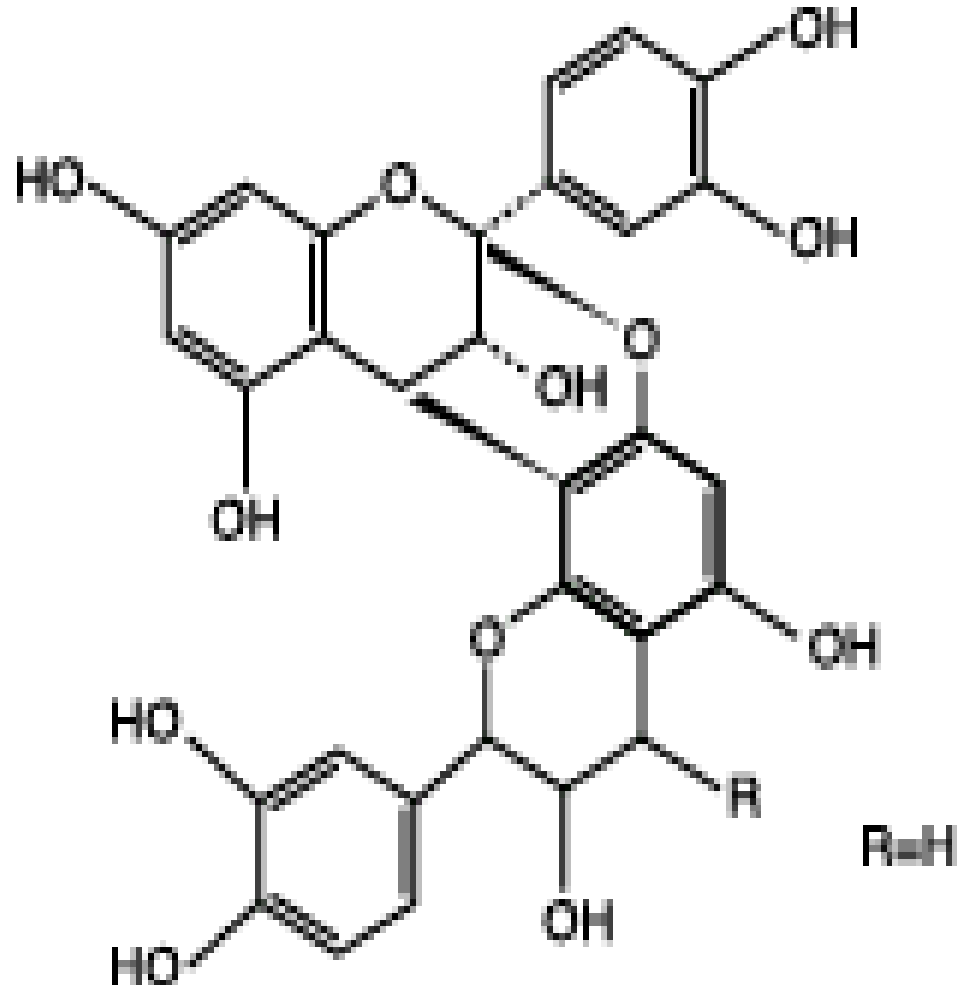




The PACs of Pacran®

Cranberry Proanthocyanidins (PACs)



Why PACs?



Proanthocyanidins (PACs)

What is the obsession with PACs?

- PACs are widely considered an active phytochemical in cranberry for urinary tract health
- The French Food Safety Authority published a urinary tract health claim based on 36 mg of North American Cranberry PACs
- The French claim has since be rejected by EFSA

Why do cranberry suppliers continue to push PACs/36 mg of PAC as *the dose* of cranberry for urinary tract health?

- Because when your product's lack product specific science you focus on the only thing you have – standardization to a marker.

AFFSA Claim Overview



The genesis of 36 mg of PACs



- Claim wording: “Cranberry can help reduce the adhesion of certain *E.coli* bacteria to the urinary tract walls”
- Generic claim published in 2004
- Daily dose: 36 mg of North American (*Vaccinium macrocarpon*) cranberry PACs
- The claim is based on the quantity of total DMAC PACs in a 300 ml glass of 27% Cranberry, Cranberry Juice Cocktail

PAC Formulation Trend

- Formulators and Brands sought out Proanthocyanidin (PAC) rich extracts to leverage the AFFSA claim.



- On December 17, 2012 all products making reference to the AFFSA health claim had to be removed from store shelves

Why was the claim rejected?

- Not because EFSA is too stringent...
- ...but due to a lack of substantiation in support of the claim

Issues with PAC only substantiation



- Method manipulation
- Adulteration
- Negative Cochrane review 2012
- New inconclusive clinical evidence published
- New evidence shows full spectrum cranberry outperforms cranberry fractions (PACs and phenolics)
- Negative EFSA opinion regarding the AFFSA claim

PAC Method of Analysis

- Methods: BL DMAC, Eur. Ph., HPLC and others
 - **Different methods yield different results**
- The spirit of the AFFSA claim is to deliver the same amount of PACs as a glass of Cranberry Juice Cocktail (CJC)
 - **A glass of CJC contains 36 mg of PACs only when measured via BL DMAC**
 - **Using other methods and reporting 36 mg of PACs is delivering $\frac{1}{4}$ - $\frac{1}{2}$ the dose**



European Pharmacopeia
36 mg of PACs
=
~1/4 of a glass of CJC



HPLC
36 mg of PACs
=
~1/2 of a glass of CJC



BL DMAC
36 mg of PACs
=
1 of a glass of CJC

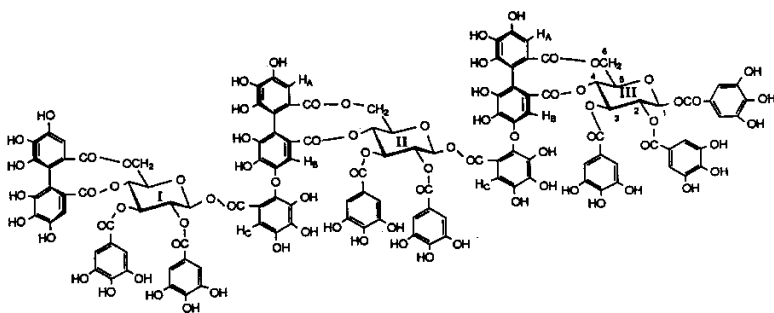
Adulteration

Cranberry PACs are unique

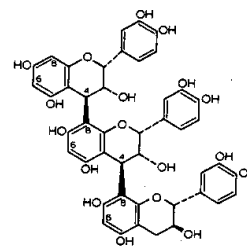
Not all PACs are created equal

- **Botanical source** – only cranberry PACs have been shown to deliver AAA
- **PAC fingerprint** – unique blends of PAC polymers deliver different levels of AAA

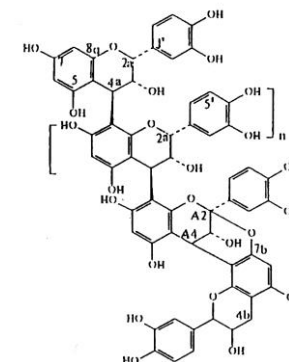
Hydrolyzable tannin (raspberry)



B-linked PAC
(grape, cocoa)



A-linked PAC (cranberry)



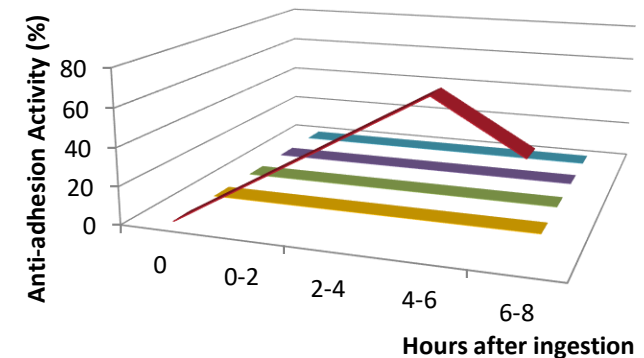
Quality of PACs: Botanical Source



Cranberry PACs deliver AAA, others do not

- PAC rich products administered
- Human urine captured at 2, 4, 6 and 8 hours after ingestion
- AAA of urine measured *Ex vivo*
- **Only urine captured post cranberry consumption exhibits AAA**

Anti-Adhesion Activity of Human Urine After Cranberry Juice and other Drinks



- Cranberry Juice cocktail
- Apple Juice
- Purple Grape Juice
- Tea
- Dark Chocolate

Independent review of cranberry juice's evidence

Cranberries for preventing urinary tract infections (Review)

Jepson RG, Williams G, Craig JC



- Reviews published in: 1998, 2004 and 2008
- 24 studies – 4473 subjects
- 14 new studies since the 2008 update
- Conclusion: "...cranberry juice cannot currently be recommended for the prevention of UTI."
- Conclusion: "Other preparations (such as powders) need to be quantified using standardized methods to ensure the potency..."

PLAIN LANGUAGE SUMMARY

Cranberries for preventing urinary tract infections

Cranberries (usually as cranberry juice) have been used to prevent urinary tract infections (UTIs). Cranberries contain a substance that can prevent bacteria from sticking on the walls of the bladder. This may help prevent bladder and other UTIs. This review identified 24 studies (4473 participants) comparing cranberry products with control or alternative treatments. There was a small trend towards fewer UTIs in people taking cranberry product compared to placebo or no treatment but this was not a significant finding. Many people in the studies stopped drinking the juice, suggesting it may not be an acceptable intervention. **Cranberry juice does not appear to have a significant benefit in preventing UTIs and may be unacceptable to consume in the long term.** Cranberry products (such as tablets or capsules) were also ineffective (although had the same effect as taking antibiotics), possibly due to lack of potency of the 'active ingredient'.

Recent CJC Studies



Recurrent Urinary Tract Infection and Urinary *Escherichia coli* in Women Ingesting Cranberry Juice Daily: A Randomized Controlled Trial

Ann E. Stapleton, MD; James Dziura, PhD; Thomas M. Hooton, MD; Marsha E. Cox, BS; Yuliya Yarova-Yarovaya, MS; Shu Chen, MS; and Kalpana Gupta, MD, MPH

- 176 participants
- Duration: 168 days
- 4 oz. cranberry juice, 8 oz. cranberry juice, or placebo
- **“Cranberry juice did not significantly reduce UTI risk compared with placebo.”**

Cranberry Juice for the Prevention of Recurrences of Urinary Tract Infections in Children: A Randomized Placebo-Controlled Trial

Jarmo Salo,¹ Matti Uhari,² Merja Helminen,³ Matti Korppi,^{3,4} Tea Nieminen,⁵ Tytti Pokka,¹ and Tero Kontiokari²
¹Department of Paediatrics, Oulu University Hospital; ²Department of Paediatrics, University of Oulu; ³Department of Paediatrics, Tampere University Hospital; ⁴Department of Paediatrics, Kuopio University Hospital; and ⁵Department of Paediatrics, Helsinki University Central Hospital, Finland

- 255 children
- Duration: one year
- 300 mL Cranberry juice or placebo
- **“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

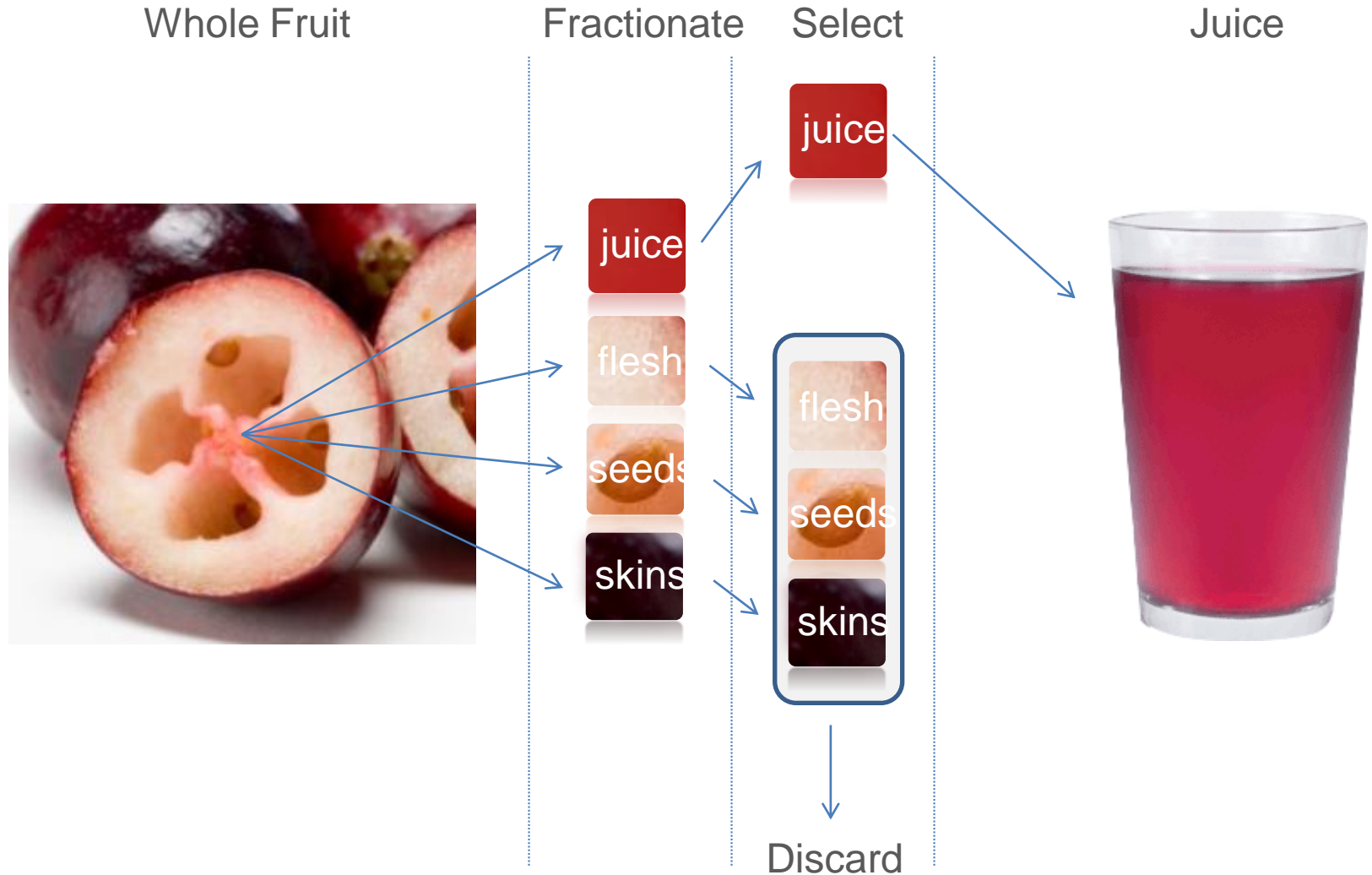
Cibele Barbosa-Cesnik,¹ Morton B. Brown,² Miatta Buxton,³ Lixin Zhang,¹ Joan DeBusscher,⁴ Betsy Foxman¹
¹Departments of ¹Epidemiology, Center for Molecular and Clinical Epidemiology of Infectious Diseases, ²BioStatistics, and ³Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan, and ⁴Department of Pathology, University of Michigan, Ann Arbor, Michigan

- 319 college age women
- Duration: 6 months
- **“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.”**

A closer look at the Ingredients



Only "a fraction" of the cranberry is used



PACs + Cranberry Synergies



The more “fractions” of cranberry the better the AAA

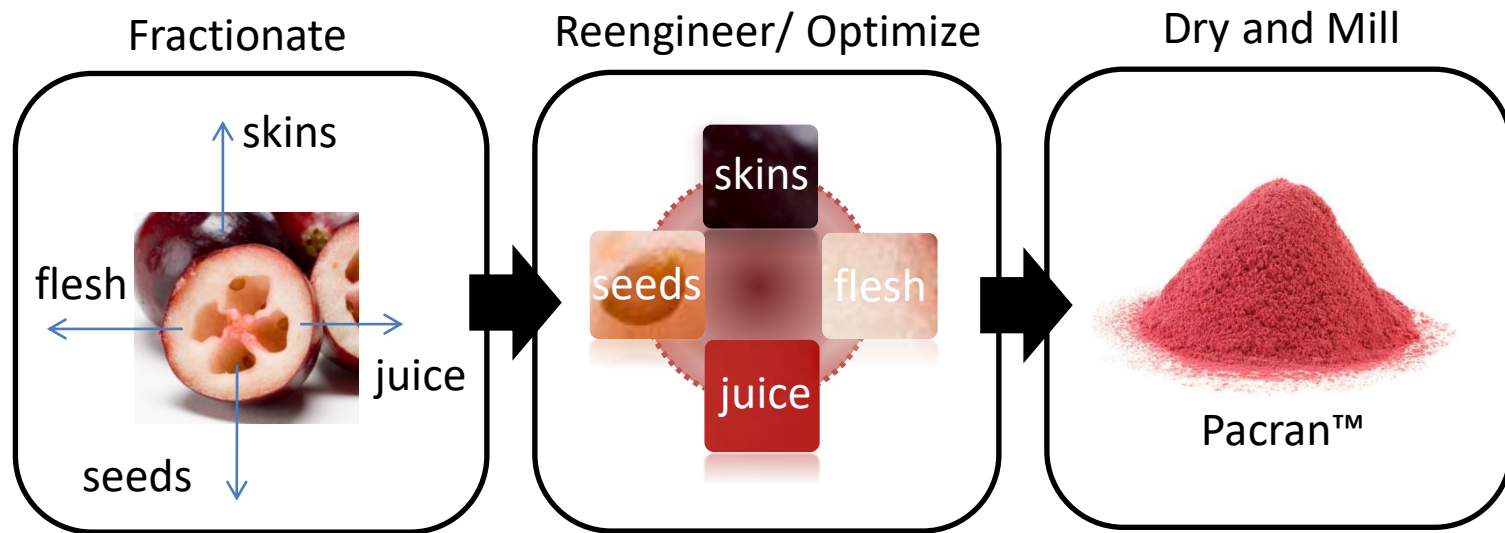
Research has shown that cranberry PACs + other active phytochemicals in cranberry work synergistically to provide superior bacterial AAA to cranberry PACs alone

Study	Product Studied	Conclusion
Impact of Cranberry Juice and Proanthocyanidins on the Ability of Escherichia coli to Form Biofilms. Food Sci. Biotechnol. 20(5): 1315-1321 (2011), Pinzón-Arango et al	Cranberry Juice Cocktail and Cranberry PAC fraction	“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 Uroepithelial Cells by Extracts from Cranberry. Journal of Medicinal Food 15 (2) 2012, 126-134 Ermel, et. al.	Cranberry PAC Fractions (Extract A & C) and Cranberry PAC Fraction + Cranberry Juice Concentrate Powder (Extract B)	“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.”

Full Spectrum Approach



Pacran® is a proprietary blend of the whole cranberry reengineered and optimized for urinary tract health



- Pacran® focuses on product specific science, not total PACs
- 500 mg / day has been clinically shown to deliver *E. coli* AAA, reduce *E. coli in vivo*, reduce recurrent UTI

Full Spectrum vs. Fractions



Pacran® Nature's formula - optimized

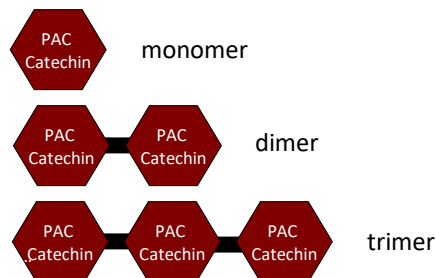
	PACran®	Cranberry Extracts	Cranberry Concentrate Powder or Cranberry Juice
Juice	X	X	X
Skins	X		
Flesh	X		
Seeds	X		
 			
PACs	X	X	X
Phenolics	X	X	X
Organic Acids	X		X
Fiber	X		
Sugar	X		X
Fatty Acids	X		
Proteins	X		
Formulation	Full Spectrum	Purified Fraction of Juice	Juice Based

The PACs of Pacran®

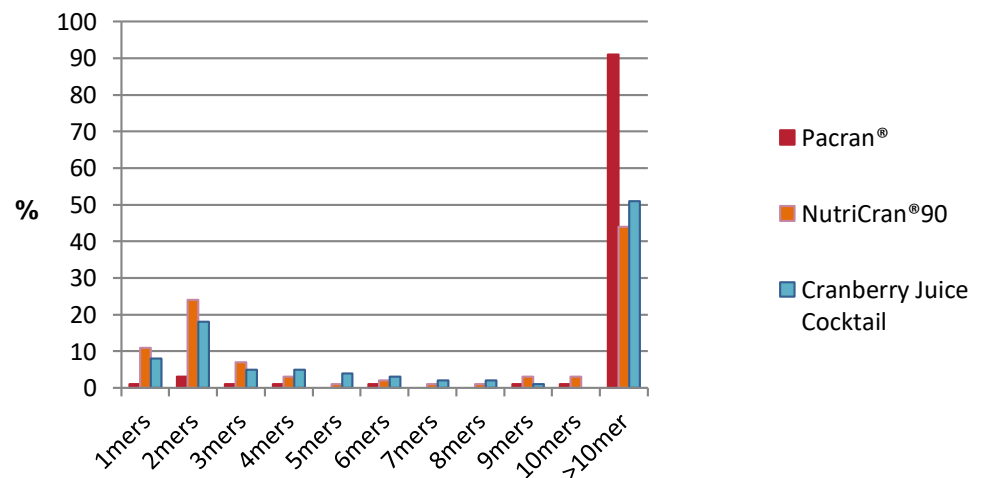


- Focus on the QUALITY of PACs not the quantity:
- Quality Level 1: North America *Vaccinium macrocarpon*
 - Pacran® is 100% *V. macrocarpon*
- Quality Level 2: Whole fruit derived PACs vs. Juice derived PACs.
 - Pacran® is made with a proprietary blend of the whole fruit providing potent, bio available, natural time release PACs and long term, consistent anti-adhesion activity

PAC Polymers



Percent PAC Polymerization

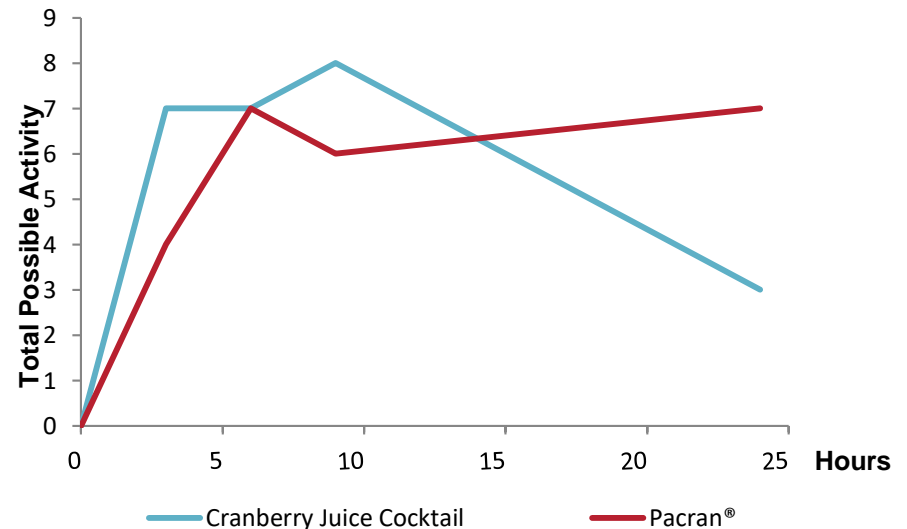


Pacran[®] vs. CJC



- 500 mg capsule of Pacran[®] (2 mg BL DMAC PACs) vs. 10 ounce serving Cranberry content of 27% (38 mg of BL DMAC PACs)
- No statistically significant differences in anti-adhesion between treatments
- Pacran[®] contains Prevention PACs that exhibit superior anti-adhesion at 24 hr. vs. CJC

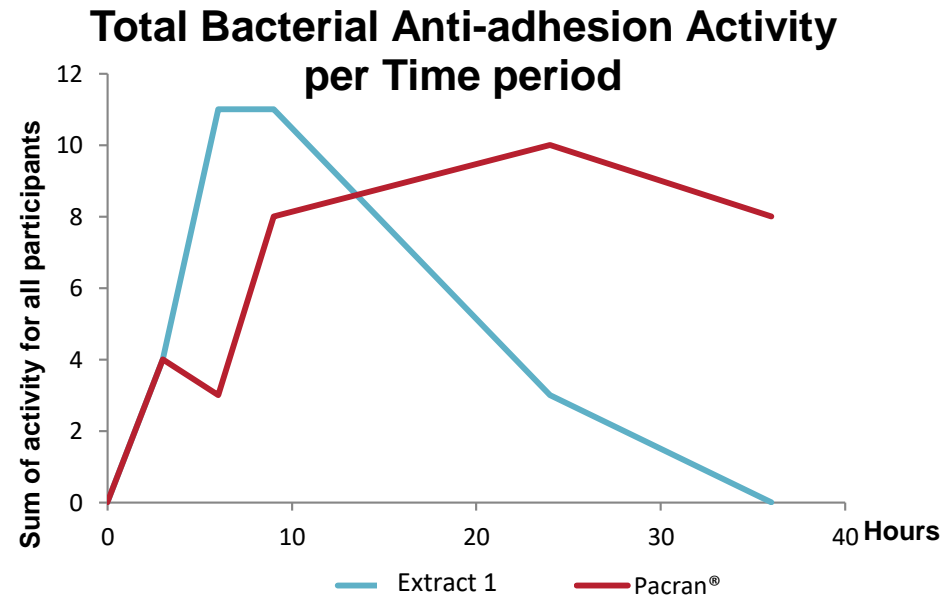
Total Anti-Adhesion Activity per Time Period



Pacran vs. Extract 1



- 500 mg capsule of Pacran® (2 mg BL DMAC PACs) vs. 2 x 650 mg capsules of Theracran (34 mg of BL DMAC PACs)
- No statistically significant differences in anti-adhesion between treatments
- Pacran® contains Prevention PACs that exhibit superior anti-adhesion at 24 and 36 hrs. vs. Extract 1



The PACs of Pacran



- Pacran's full spectrum formulation delivers the right balance of PAC polymers and cranberry phytochemicals
- Pacran delivers the same or better *E. coli* anti-adhesion activity as products with 17-19 times the PACs

Pacran doesn't focus on PACs because it focuses on efficacy

Pacran specific substantiation:

- Shown to provide *E. coli* AAA *Ex vivo*
- Shown to reduce *E. coli* *in vivo*
- Shown to reduce UTI recurrence rates
- Health claims