ANTHOCRAN® phytosome

indena®
SCIENCE IS OUR NATURE. SINCE 1921
100 YEARS

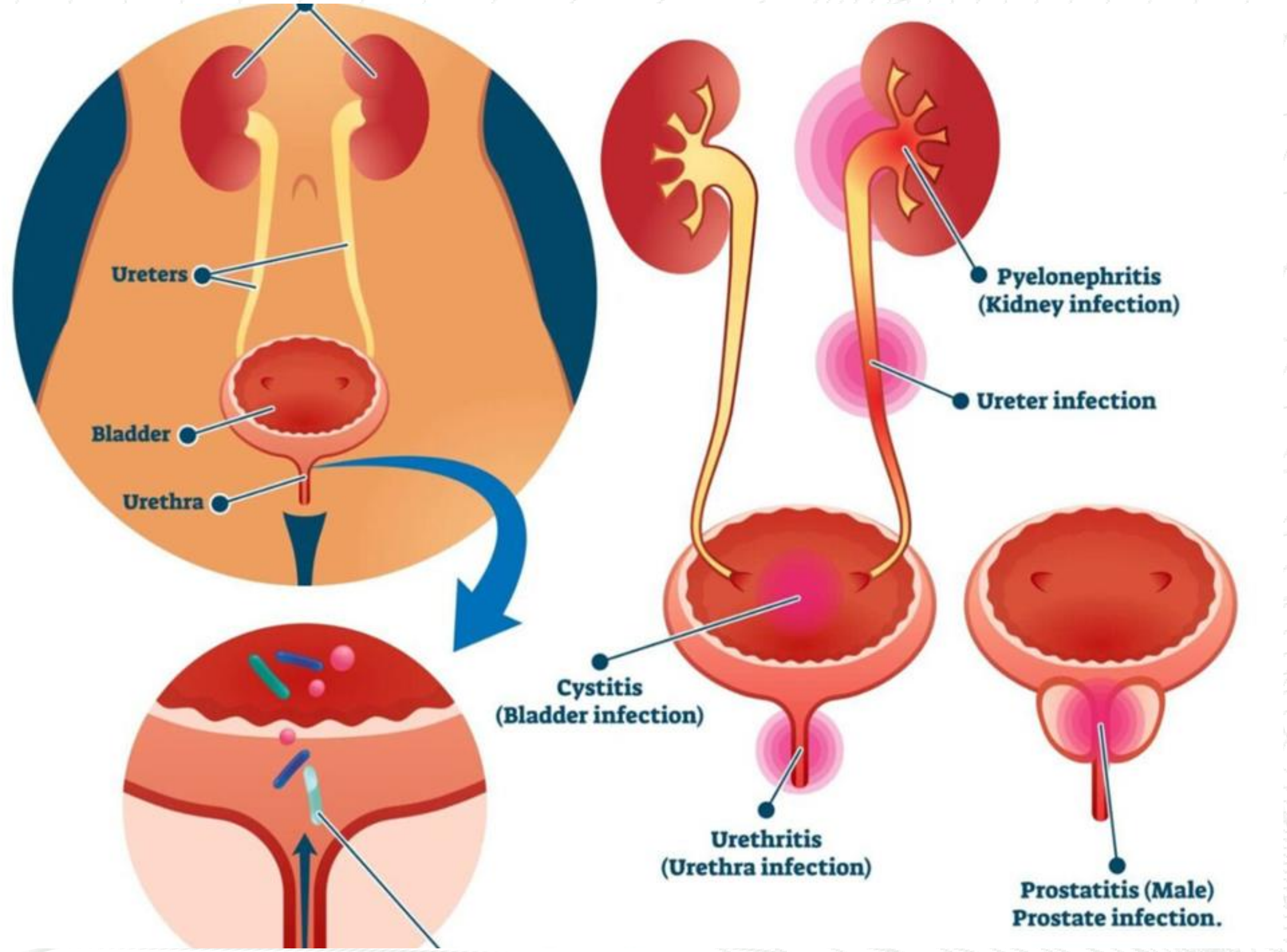
# New & more bioavailable cranberry extract

Serena Tongiani, Chief Product Portfolio  Indena Spa
*serena.tongiani@indena.com*

Vitafoods Europe
10-12 May 2022 Geneva
2-13 May 2022 Online

## A urinary tract infection (UTI) can affect any part of the urinary system, kidneys, bladder or urethra.

More than 150 million people globally suffer from urinary tract infections, and about 30% will have a recurrent infection within 6 months. mostly women.
Symptoms include frequent, painful urination, pelvic pain and traces blood in the urine.




https://emedprimarycare.com/urinary-tract-infections/
Emed Jacksonville, Florida

## CRANBERRY
## (*Vaccinium macrocarpon*)
## EXTRACT

The cranberry is one of the most thoroughly studied foods for the prevention of urinary tract infections. It is a rich source of polyphenols, including the unique A-type proanthocyanidins, but is now an evidence that the activity goes beyond the PAC content

For a UTI to occur, bacteria must adhere to and invade the lining of the bladder. Cranberries extract contains specific compounds which interfere with the bacteria's ability to the bladder wall, reducing the likelihood of infection.

ANTHOCRAN® phytosome

NEW
New & More Effective

## Pre-1800s

First anecdotal medical use of cranberries associated with Native American tribes

## 1801

Cranberries introduced into American medical practice as an anti-scorbutic, laxatic, and anti-pyretic

## 1905

Topical use of cranberry noted by *King's American Dispensatory* to ameliorate inflammation, swelling, and ulcers

## 1984

Cranberry juice reported to inhibit the adherence of *E. coli* and other gram-negative bacteria to epithelial cells.

## 1994

The first randomized, double-blind, placebo-controlled clinical trial investigating the treatment and preventative effects of cranberry juice in bacteriuria and pyuria

## 1998

Addition of cranberry to growth medium of P-fimbriated *E. coli* causes loss of adhesion and loss of fimbriae correlated with incubation time

## 2000

The structure of cranberry proanthocyanidins (PACs) are described in detail

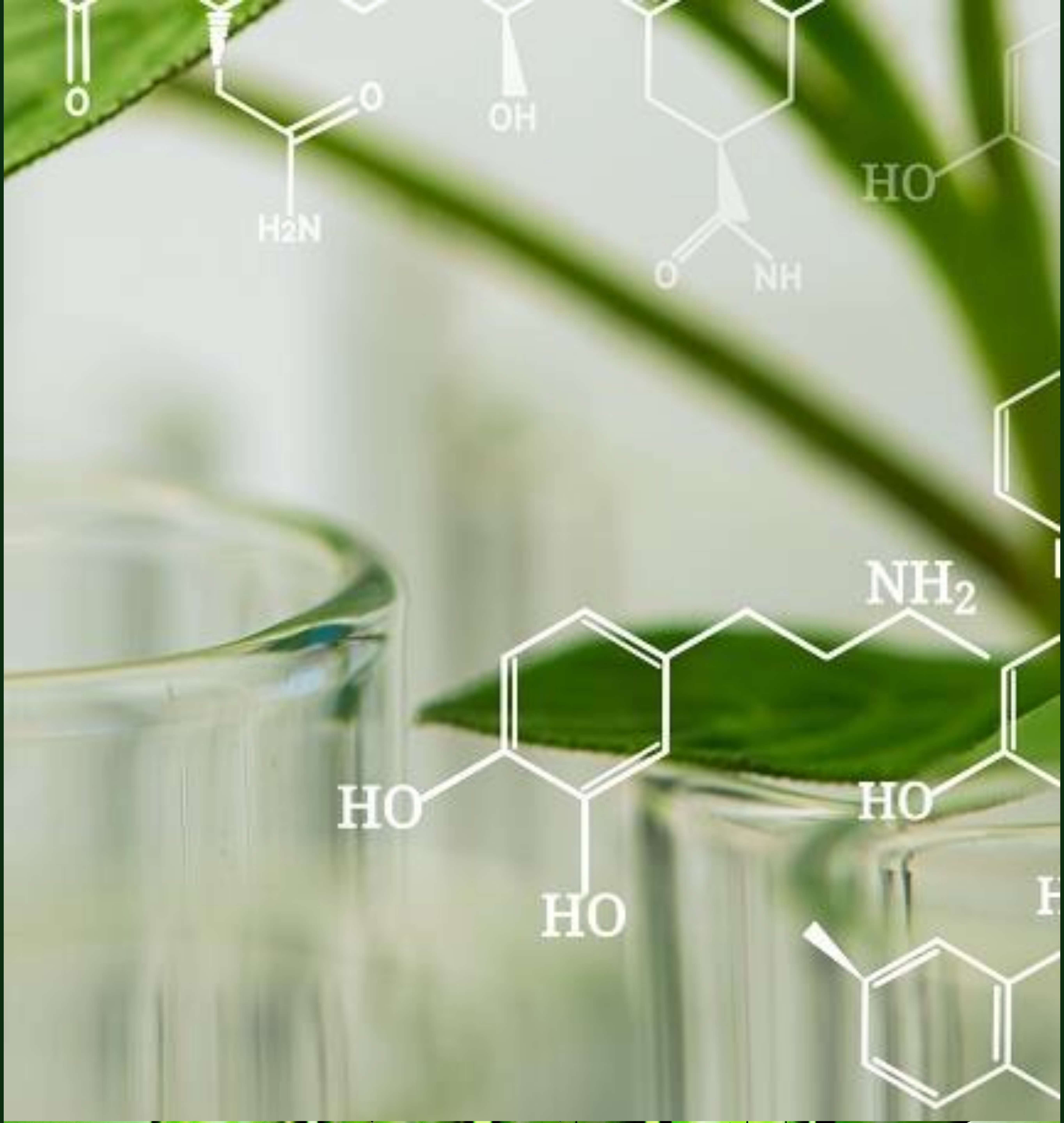
## 2020

NEW ACTIVE METABOLITES IDENTIFIED AFTER ANTHOCRAN® INTAKE

*American Herbal Pharmacopoeia™ • Cranberry Fruit • 2002*

ANTHOCRAN® phytosome

# FULL PHYTOCHEMICAL CHARACTERIZATION

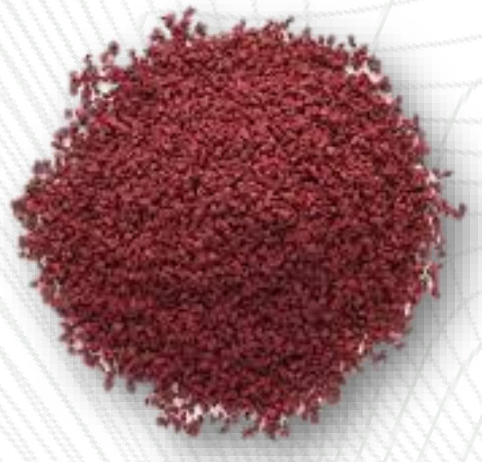


# INDENA EXPERTISE AT THE SERVICE OF QUALITY AND INNOVATION

**CONCENTRATED JUICE**

**Shipment at – 20° C**

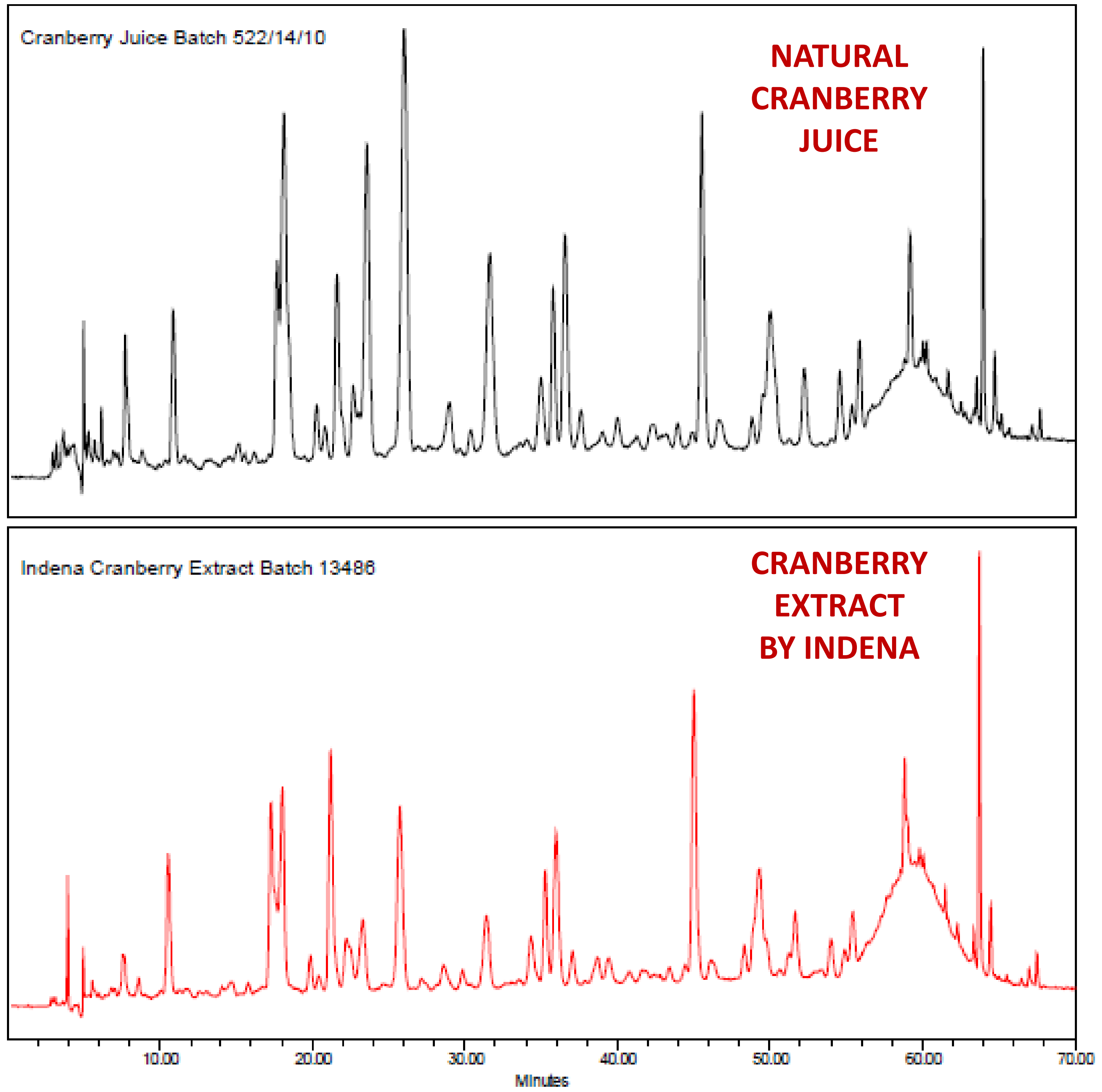
**INDUSTRIAL MANUFACTURE OF THE STANDARDIZED EXTRACT IN INDENA PRODUCTION SITE (Tours - France)**

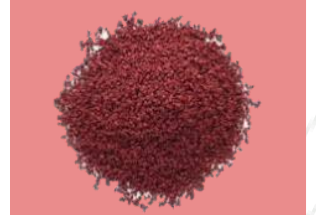


**APPLICATION OF PHYTOSOME® TECHNOLOGY**

ANTHOCRAN® phytosome

**INDENA CRANBERRY EXTRACT MAINTAINS THE SAME PHYTOCHEMICAL PROFILE OF NATURAL CRANBERRY JUICE**



ANTHOCRAN® phytosome

# THE FULL SPECTRUM OF POLYPHENOLS

### FLAVONOLS, FLAVANOLS AND PACs

Scopoletin
Kaempferol
Epicatechin
Catechin
Quercetin
Epigallocatechin
Gallocatechin
Isorhamnetin
Myricetin
3′-O-methylmyricetin
Syringetin
Quercetin-3-O-arabinofuranoside
Quercetin-3-O-arabinopyranoside
Quercetin-3-O-xylopyranoside
Catechin-3-O-gallate
Epicatechin-3-O-gallate
Kaempferol-7-O-glucoside
Isorhamnetin-3-O-arabinofuranoside
Isorhamnetin-3-O-xylopyranoside
Isorhamnetin-3-O-arabinopyranoside
Quercetin-3-O-rhamnoside
Myricetin-3-O-arabinofuranoside
Myricetin-3-O-arabinopyranoside
Myricetin-3-O-xylopyranoside
Quercetin 3-O-glucoside
Quercetin-3-O-galactoside
Isorhamnetin-3-O-glucopyranoside
Isorhamnetin-3-O-glucofuranoside
Isorhamnetin-3-O-galactoside
Syringetin-3-O-arabinofuranoside
Syringetin-3-O-xylopyranoside
Syringetin-3-O-arabinopyranoside
Myricetin-3-O-glucoside
Myricetin-3-O-galactoside
Syringetin-3-O-rhamnoside
Proanthocyanidin A-type dimer
Proanthocyanidin B-type dimer
Proanthocyanidin A-type trimer
Proanthocyanidin B-type trimer

### ANTHOCYANINS

Cyanidin
Peonidin
Cyanidin-3-O-arabinoside
Peonidin-3-O-arabinoside
Cyanidin-3-O-galactoside
Cyanidin-3-O-glucoside
Petunidin-3-O-arabinoside
Peonidin-3-O-galactoside
Peonidin 3-O-glucoside
Malvidin-3-O-galactoside
Malvidin-3-O-glucoside

### PHENOLIC ACIDS

Benzoic acid
Protocatechuic acid
*p*-Coumaric acid
Gallic acid
Caffeic acid
Ferulic acid
Sinapinic acid
Caffeoyl glucose
Chlorogenic acid

ANTHOCRAN® phytosome

**CONTAINS THE FULL POLYPHENOLS PROFILE OF NATURAL CRANBERRY, NOT ONLY PACs**

Baron, Giovanna, et al. "Profiling Vaccinium macrocarpon components and metabolites in human urine and the urine ex-vivo effect on Candida albicans adhesion and biofilm-formation." *Biochemical pharmacology* 173 (2020): 113726.

100 YEARS

# WHAT IS ANTHOCRAN® phytosome

New health-food ingredient based on the formulation of **Indena proprietary cranberry extract Anthocran with Phytosome® technology**.

Standardized in **proanthocyanidins: 6.0-9.0%** UV-visible spectrophotometric contents (DMAC method).

Suggested dose: **120 mg/day**

ANTHOCRAN® phytosome

CRANBERRY
(*Vaccinium macrocarpon*)
EXTRACT

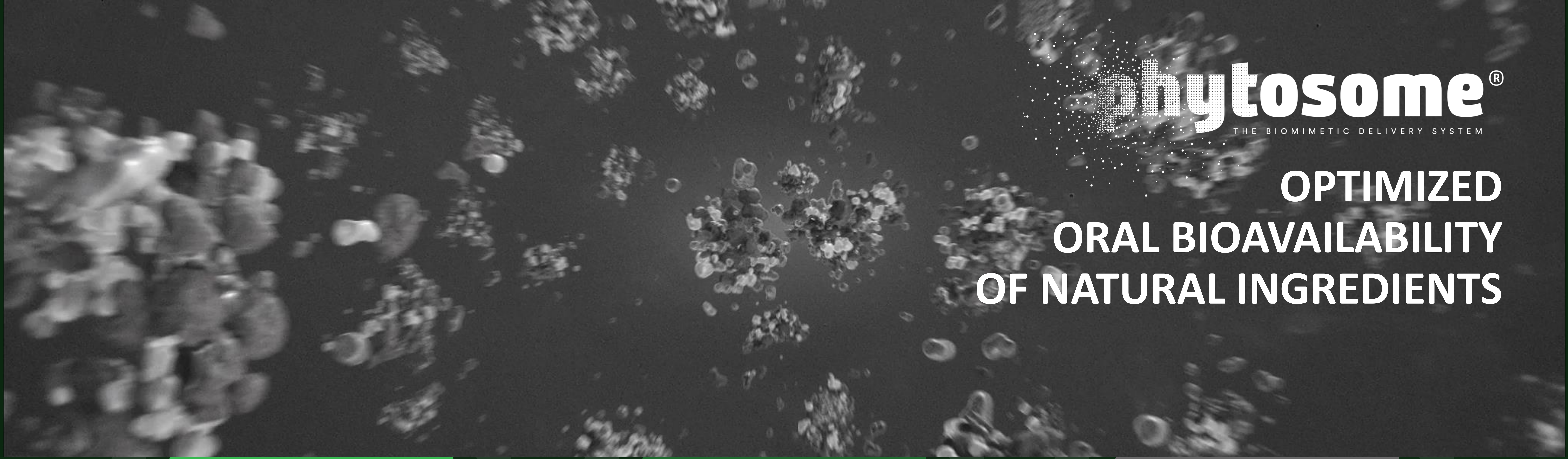
\+ phytosome™ THE BIOMIMETIC DELIVERY SYSTEM

INDENA TECHNOLOGY TO IMPROVE BIOAVAILABILITY

=

HEALTH FOOD INGREDIENT

100 YEARS



phytosome®
THE BIOMIMETIC DELIVERY SYSTEM

# OPTIMIZED ORAL BIOAVAILABILITY OF NATURAL INGREDIENTS

## 1 NATURAL INGREDIENT

Health benefits

## 2 LECITHIN

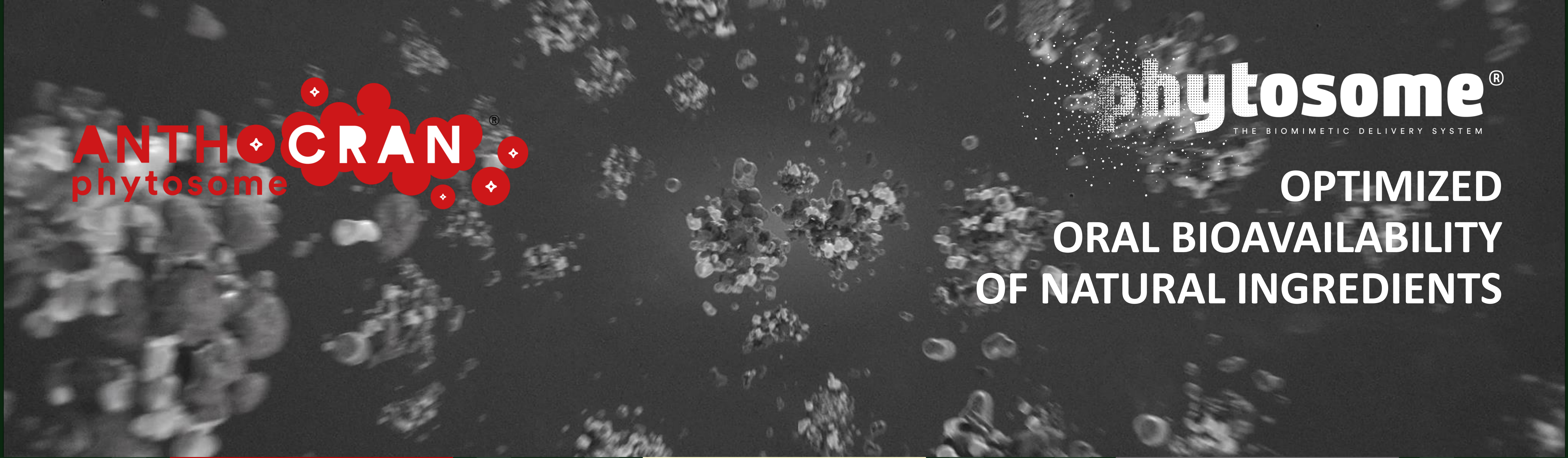
Inhibition of self-aggregation

## 3 FOOD ADDITIVES

Improvement of technological properties (e.g. density, flowability)

Phytosome® is a solid dispersion of botanicals or natural compounds into a 100% food-grade matrix based on lecithin, amphipathic molecules which act as inhibitor of self-aggregation and effective wetting agents.

100 YEARS




1

CRANBERRY EXTRACT

2

SUNFLOWER LECITHIN

3

ADDITIVES FREE

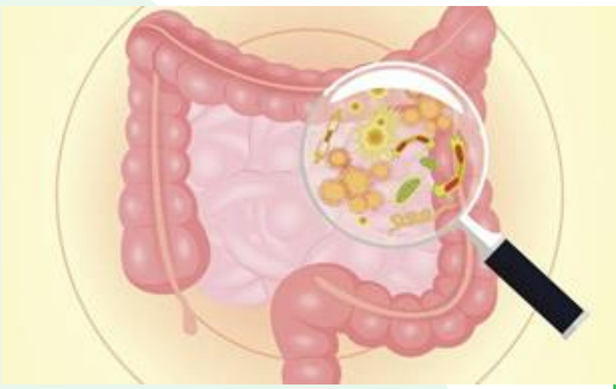
MANUFACTURING SOLVENT: ETHYL ACETATE

100 YEARS

# ANTHOCRAN® phytosome: THE ROAD MAP

URINARY HUMAN PHARMACOKINETICS

NEW PACs METABOLITES FIRSTLY DESCRIBED IN HUMAN URINE



INTERACTION WITH HUMAN MICROBIOTA

EVIDENCE OF POSITIVE INTERACTIONS WITH CRANBERRY POLYPHENOLS

1

2

3

4

DEVELOPMENT OF CRANBERRY EXTRACT AND ITS PHYTOSOME® FORMULATION

FORMULATION DESIGN

PREVENTION OF RECURRENT UTIs AFTER CATHETERIZATION

HUMAN EFFICACY STUDY

100 YEARS

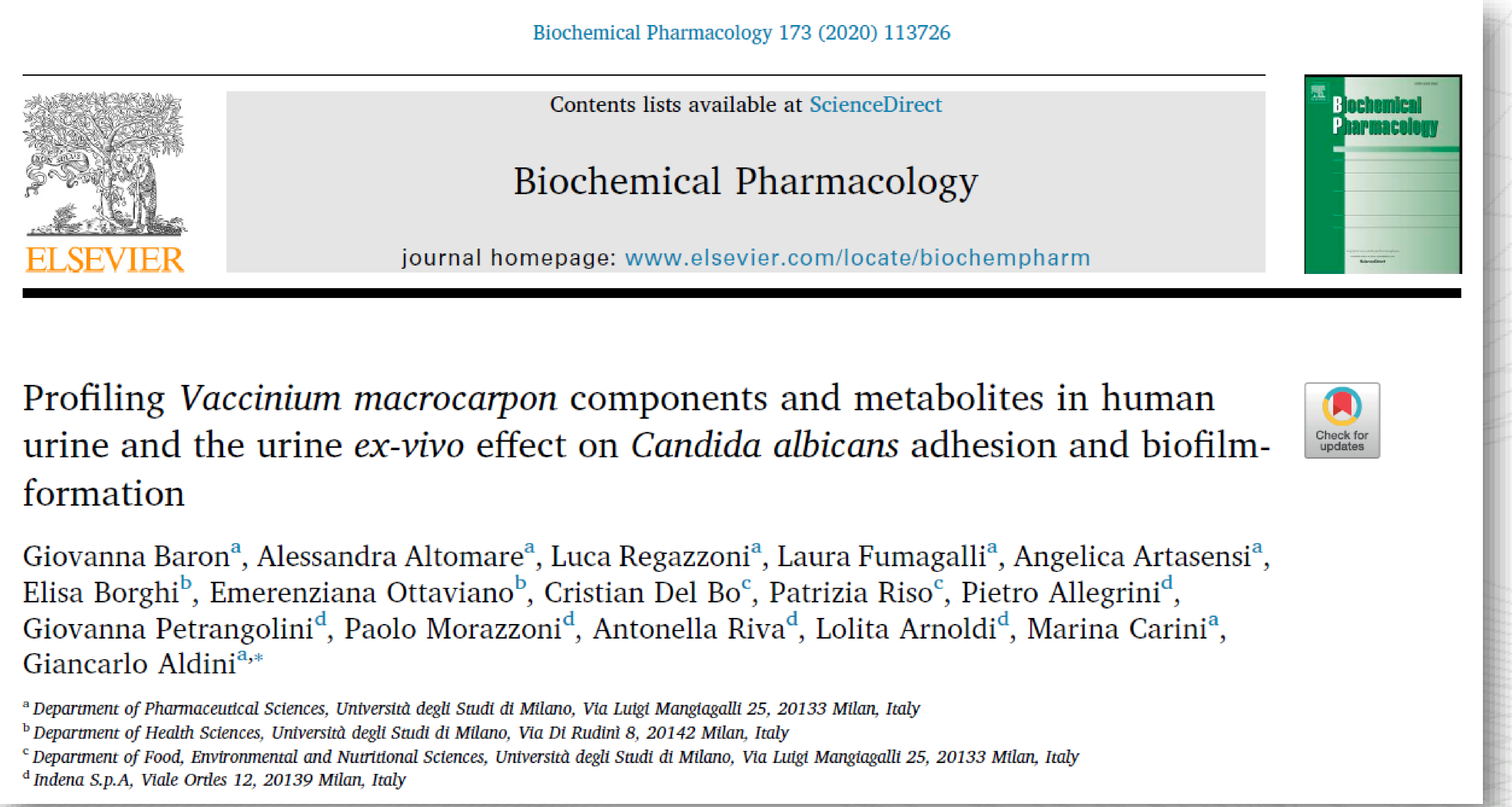
ANTHOCRAN® phytosome

# HUMAN URINE PK STUDY

ANTHOCRAN® phytosome

# HUMAN URINE PK STUDY

## INGREDIENTS MEANT TO TREAT URINARY TRACT INFECTIONS (UTIs) NEED TO BE FOUND IN THE URINE RATHER THAN IN THE PLASMA



Biochemical Pharmacology 173 (2020) 113726

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Biochemical Pharmacology

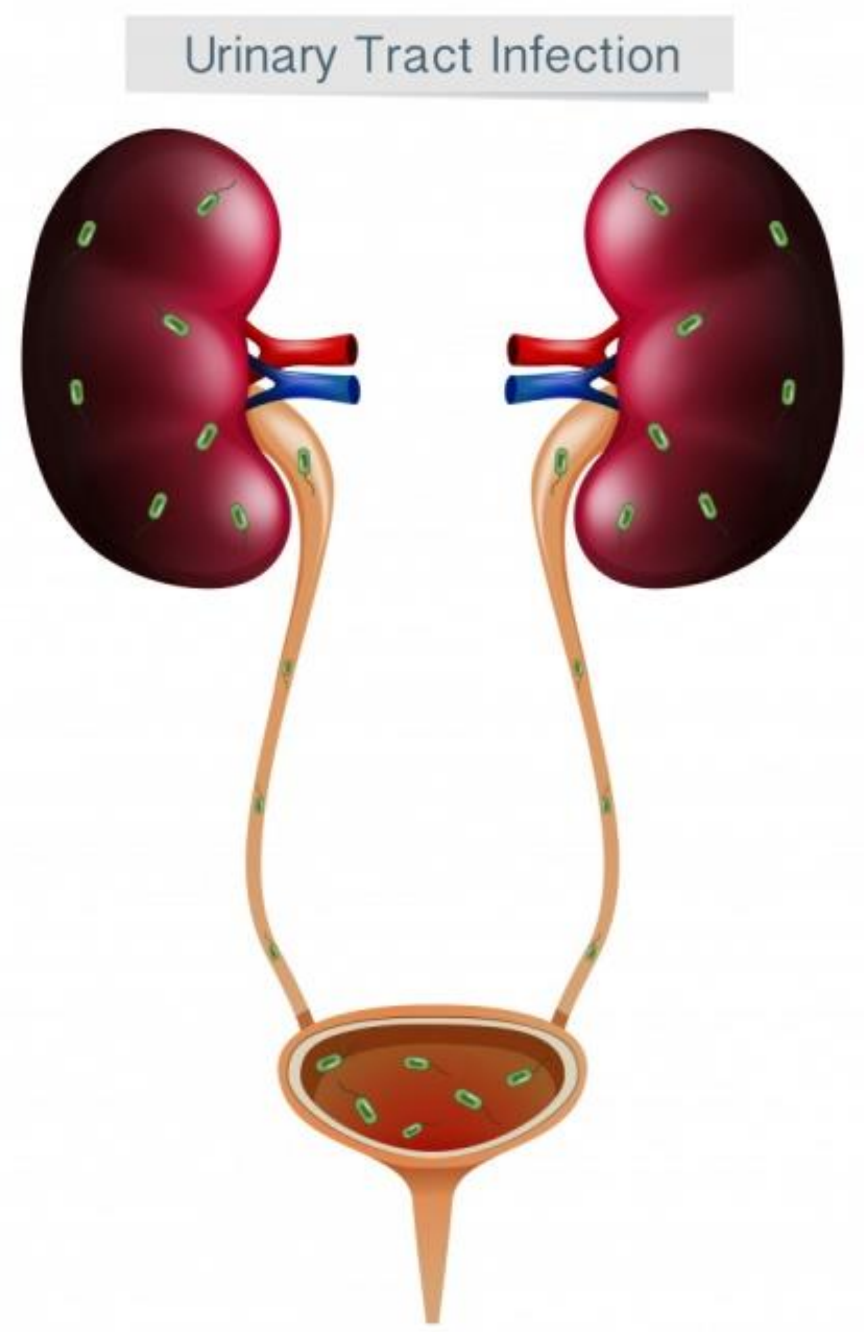
journal homepage: www.elsevier.com/locate/biochempharm

ELSEVIER

Profiling *Vaccinium macrocarpon* components and metabolites in human urine and the urine *ex-vivo* effect on *Candida albicans* adhesion and biofilm-formation

Giovanna Baron[a], Alessandra Altomare[a], Luca Regazzoni[a], Laura Fumagalli[a], Angelica Artasensi[a], Elisa Borghi[b], Emerenziana Ottaviano[b], Cristian Del Bo[c], Patrizia Riso[c], Pietro Allegrini[d], Giovanna Petrangolini[d], Paolo Morazzoni[d], Antonella Riva[d], Lolita Arnoldi[d], Marina Carini[a], Giancarlo Aldini[a,*]

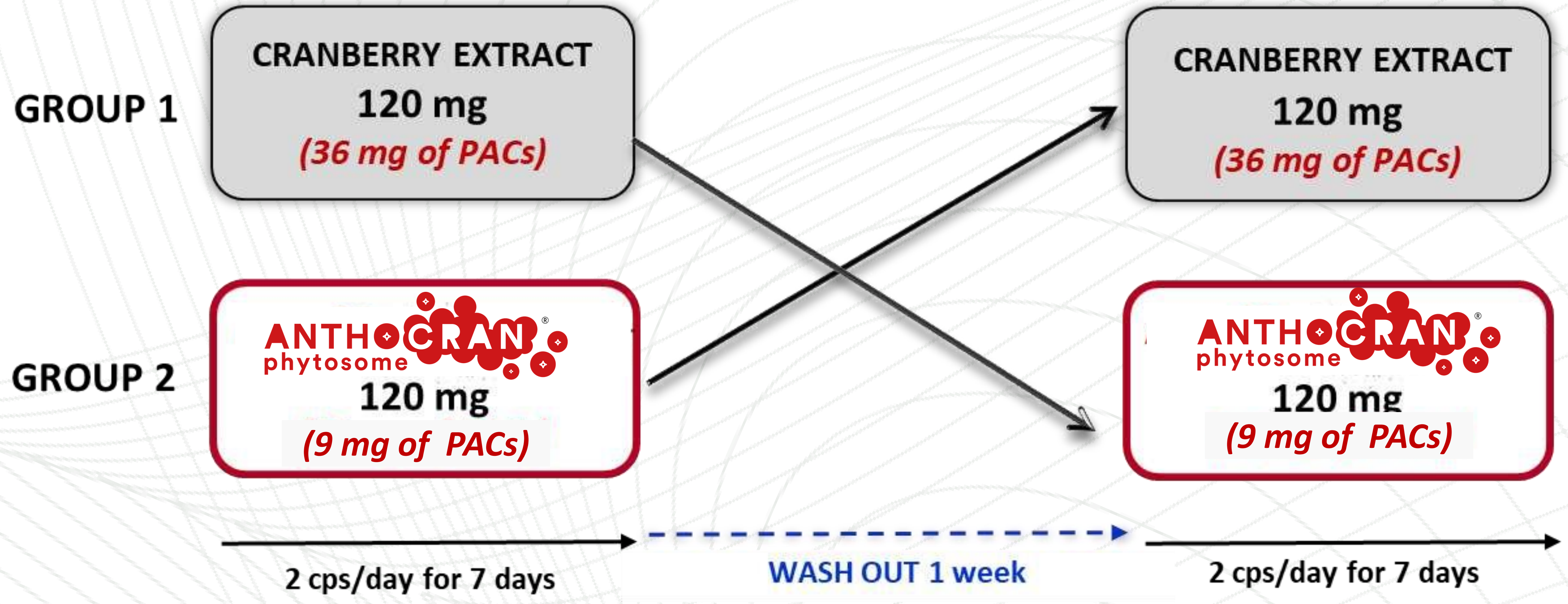
[a] Department of Pharmaceutical Sciences, Università degli Studi di Milano, Via Luigi Mangiagalli 25, 20133 Milan, Italy
[b] Department of Health Sciences, Università degli Studi di Milano, Via Di Rudinì 8, 20142 Milan, Italy
[c] Department of Food, Environmental and Nutritional Sciences, Università degli Studi di Milano, Via Luigi Mangiagalli 25, 20133 Milan, Italy
[d] Indena S.p.A, Viale Ortles 12, 20139 Milan, Italy




100 YEARS

Baron, Giovanna, et al. "Profiling Vaccinium macrocarpon components and metabolites in human urine and the urine ex-vivo effect on Candida albicans adhesion and biofilm-formation." *Biochemical pharmacology* 173 (2020): 113726.

# STUDY DESIGN AND OBJECTIVES




- **STUDY DESIGN:** randomized, cross-over, double-blind
- **POPULATION:** 13 healthy volunteers (**women**, age 25±4 years, BMI 26.6±2.0 kg/m$^2$)
- **FORMULATION A:** ANTHOCRAN 120 mg (=**36 mg** of PACs)
- **FORMULATION B:** ANTHOCRAN phytosome 120 mg (=**9 mg** of PACs)
- **SAMPLING:** day 0 and day 7 (at 1, 2, 4, 6, 10, 12, 24h)

## STUDY ENDPOINTS:

### #1 FULL IDENTIFICATION OF CRANBERRY COMPOUNDS AND METABOLITES IN URINE

- **Which cranberry components are found in urine?**
- **Do proanthocyanidins (PACs) reach the urine?**
- **If not, what is responsible for cranberry-acknowledged health benefits in UTIs?**

### #2 ACTIVITY AGAINST *CANDIDA ALBICANS*

- **Is Anthocran® Phytosome® effective against adhesion and biofilm formation of *Candida albicans* clinical isolates (*Ex vivo effect*)?**
- **Is Anthocran Phytosome® as effective as Anthocran®, despite the lower content of PACs (9 mg vs. 36 mg) in the same unitary dose?**

100 YEARS

Baron, Giovanna, et al. "Profiling Vaccinium macrocarpon components and metabolites in human urine and the urine ex-vivo effect on Candida albicans adhesion and biofilm-formation." Biochemical pharmacology 173 (2020): 113726.

# THE *RIGHT* PK STUDY:

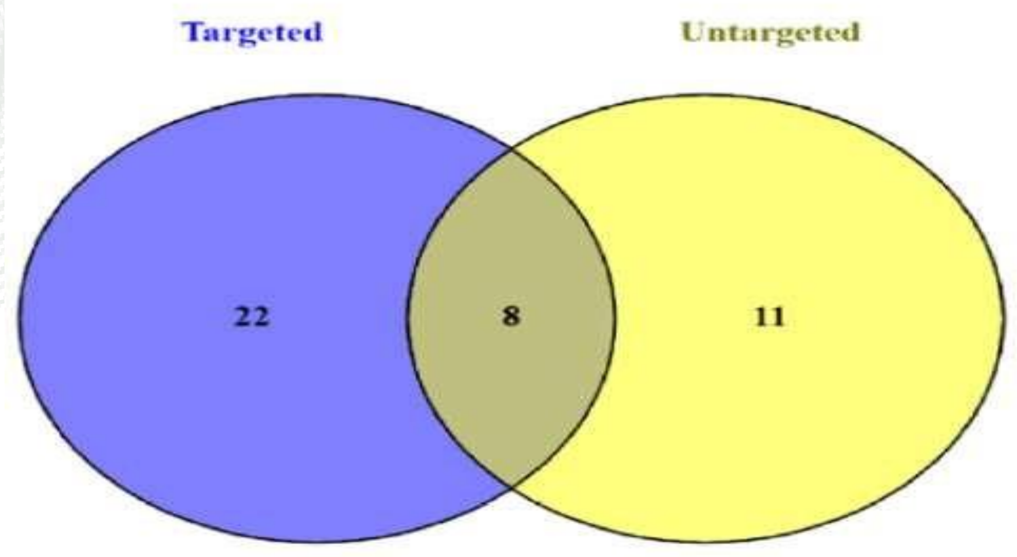
# POLYPHENOL PROFILE IN HUMAN URINE

## A DEEP, DOUBLE INVESTIGATION WITH 2 DIFFERENT METHODS ALLOWED FOR THE IDENTIFICATION OF 42 COMPOUNDS IN HUMAN URINE, INCLUDING NEW ONES

**TARGETED ANALYSIS**: searching in urine samples for the compounds listed in an in-house database (total number of compounds = 138)

<table>
<tr><th>Targeted</th><th>Untargeted</th></tr>
<tr><td colspan="2">Sinapinic acid</td></tr>
<tr><td colspan="2">3,4-dihydroxyhydrocinnamic acid</td></tr>
<tr><td colspan="2">p-Hydroxyhippuric acid</td></tr>
<tr><td colspan="2">m-Hydroxyhippuric acid</td></tr>
<tr><td colspan="2">o-Hydroxyhippuric acid (salicyluric acid)</td></tr>
<tr><td colspan="2">5-(3',4'-dihydroxyphenyl)-γ-valerolactone</td></tr>
<tr><td colspan="2">5-(3',4'-dihydroxyphenyl)-γ-valerolactone-4'-O-sulphate</td></tr>
<tr><td colspan="2">Dihydroxyhydrocinnamic acid-3-O-glucuronide</td></tr>
<tr><td>Protocatechuic acid</td><td>Quinic acid</td></tr>
<tr><td>p-Coumaric acid</td><td>2-methylhippuric acid</td></tr>
<tr><td>Gallic acid</td><td>5-(3',4'-dihydroxyphenyl)-γ-valerolactone-3'-O-sulphate</td></tr>
<tr><td>Kaempferol</td><td>5-(3',4',5'-trihydroxyphenyl)-γ-valerolactone-3'-O-sulphate</td></tr>
<tr><td>Quercetin</td><td>4-Hydroxy-5-(dihydroxyphenyl)-valeric acid-O-sulphate</td></tr>
<tr><td>Syringetin</td><td>Salicyluric glucuronide</td></tr>
<tr><td>Quercetin-3-O-arabinofuranoside</td><td>3-O-Methylcatechin-sulphate</td></tr>
<tr><td>Quercetin 3-O-rhamnoside</td><td>5-(3',4'-dihydroxyphenyl)-γ-valerolactone-3'-O-glucuronide</td></tr>
<tr><td>Quercetin-3-O-galactoside</td><td>5-(3',4'-dihydroxyphenyl)-γ-valerolactone-4'-O-glucuronide</td></tr>
<tr><td>2-hydroxybenzoic acid</td><td>Sinapinic glucuronide</td></tr>
<tr><td>3-hydroxybenzoic acid</td><td>5-(3',4'-dihydroxyphenyl)-γ-valerolactone sulphoglucuronide</td></tr>
<tr><td>4-hydroxybenzoic acid</td><td></td></tr>
<tr><td>2,3-dihydroxybenzoic acid</td><td></td></tr>
<tr><td>2,5-dihydroxybenzoic acid</td><td></td></tr>
<tr><td>2,4-dihydroxybenzoic acid</td><td></td></tr>
<tr><td>3-(4-hydroxyphenyl)-propionic acid</td><td></td></tr>
<tr><td>3,4-dihydroxyphenylacetic acid</td><td></td></tr>
<tr><td>Hippuric acid</td><td></td></tr>
<tr><td>Isorhamnetin-3-O-arabinopyranoside</td><td></td></tr>
<tr><td>4-methylcatechol-O-sulphate</td><td></td></tr>
<tr><td>Pyrogallol-O-2-sulphate</td><td></td></tr>
<tr><td>Vanillic acid-4-O-sulphate</td><td></td></tr>
</table>

**UNTARGETED ANALYSIS:** searching for ions present in urine samples collected after cranberry consumption, that were not present in the pre-treatment sample (MS/MS)



# IDENTIFICATION OF COMPOUNDS FIRST DESCRIBED IN HUMAN URINE

## ANTHOCRAN TREATMENT LEADS TO THE IDENTIFICATION OF COMPOUNDS RESPONSIBLE FOR CRANBERRY-ACKNOWLEDGED CLINICAL EVIDENCE IN UTIs

| | | |
|---|---|---|
| **PACs (A and B type)** | **NOT DETECTED** | **A-type are considered to be related to cranberry activity in UTIs, but evidence for this in the literature is inconclusive**<br>**Lack of detection in urine is in agreement with literature**<br>Degraded into phenolic compounds by human microbiota in the colon |
| ANTHOCYANINS | LACK OF DETECTION | Possible biotransformation mediated by colonic microflora into small phenolic compounds |
| FLAVONOLS | LOW ABOUNDANCE OF GLYCOSYLATED FORMS | Low abundance of glycosylated forms due to enzymatic hydrolysis into corresponding aglycones, taking place in the intestine<br>Aglycones can be transformed into phenolic acids by C-ring cleavage and/or undergo phase-II metabolism |
| NEW<br>**VALEROLACTONES AND VALERIC ACIDS** | **IDENTIFIED IN HUMAN URINE FOR THE FIRST TIME** | **Known as PACs metabolites, but never identified in urine after cranberry intake**<br>**Reports suggest that the biotransformation of PACs to valerolactones is driven by gut microbiota** |

100 YEARS

Baron, Giovanna, et al. "Profiling Vaccinium macrocarpon components and metabolites in human urine and the urine ex-vivo effect on Candida albicans adhesion and biofilm-formation." *Biochemical pharmacology* 173 (2020): 113726.

# INTERACTION WITH HUMAN MICROBIOTA

# ANTHOCRAN® phytosome

# *EX VIVO* STUDY DESIGN

Food Research International 141 (2021) 110137

Contents lists available at ScienceDirect

Food Research International

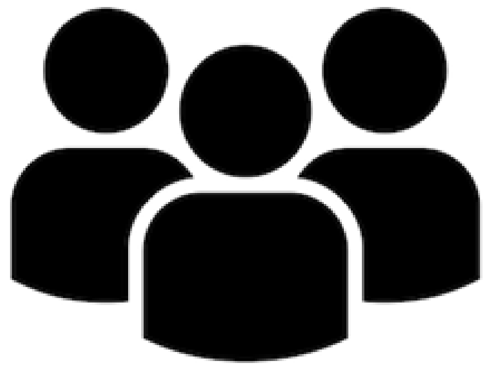
journal homepage: www.elsevier.com/locate/foodres

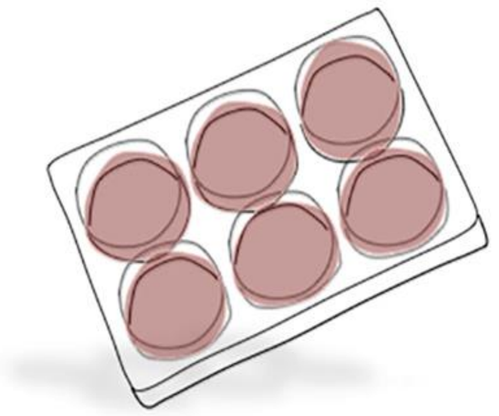
ELSEVIER

*In vitro* (poly)phenol catabolism of unformulated- and phytosome-formulated cranberry (*Vaccinium macrocarpon*) extracts

Letizia Bresciani[a,1], Giuseppe Di Pede[b,1], Claudia Favari[b], Luca Calani[c], Veronica Francinelli[b], Antonella Riva[d], Giovanna Petrangolini[d], Pietro Allegrini[d], Pedro Mena[b,*], Daniele Del Rio[a]

[a] Department of Veterinary Science, University of Parma, Via Volturno, 39 - 43125 Parma, Italy
[b] Department of Food and Drug, University of Parma, Via Volturno, 39 - 43125 Parma, Italy
[c] Department of Food and Drug, University of Parma, Parco Area delle Scienze 27/A, 43124 Parma, Italy
[d] Research and Development Department, Indena S.p.A., Viale Ortles, 12 – 20139 Milano, Italy





**3 HEALTHY SUBJECTS** (2 men and 1 woman):

- no antibiotics for previous 3 months
- no-polyphenols diet for 2 days prior to faecal collection

**FAECAL SLURRY FERMENTED FOR 24h WITH** (samples standardized for PACs content):

- unformulated cranberry extract
- ANTHOCRAN® phytosome

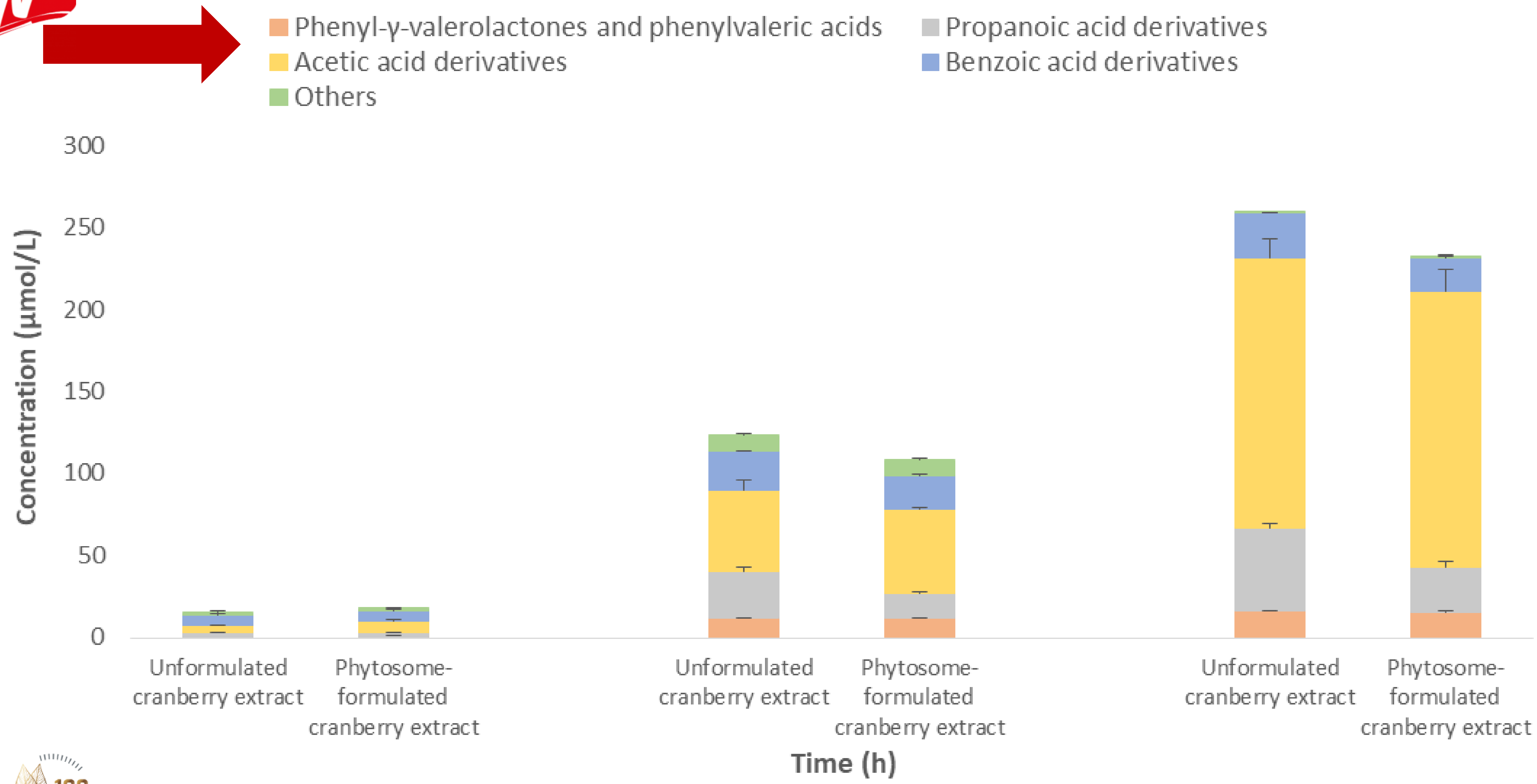
**UHPLC-LIT-MS$^n$ ANALYSIS OF:**

- production of cranberry metabolites

100 YEARS

Bresciani, Letizia, et al. "In vitro (poly) phenol catabolism of unformulated-and phytosome-formulated cranberry (Vaccinium macrocarpon) extracts." Food Research International 141 (2021): 110137.

# PRODUCTION OF METABOLITES WITH BIOLOGICAL ACTIVITY




**Anthocran® had significantly higher production of metabolites linked to phenylpropanoic and benzoic acid derivatives.**

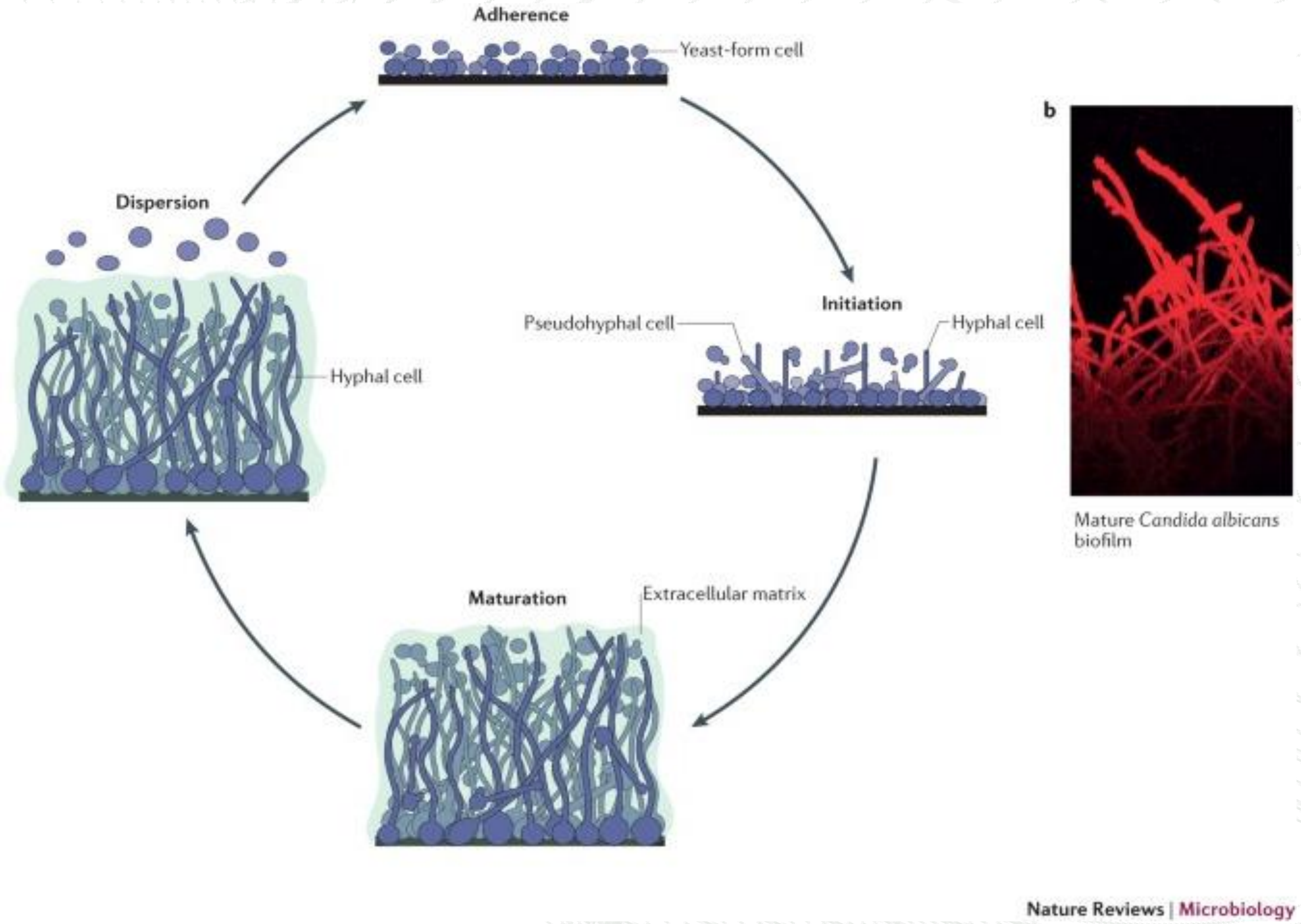
**Anthocran Phytosome® in comparison could be metabolized slowly at colonic level in comparison to Anthocran®.**

**Comparable concentration of metabolites after 24 hrs suggests the Phytosome® does not interfere with physiological polyphenol degradation.**

Bresciani, et al. (2021)

# UTIs: DON'T FORGET CANDIDURIA (*Candida albicans* INFECTION)

FORMATION OF CANDIDA ALBICANS BIOFILMS




The presence of *Candida* spp. in urines (i.e. candiduria) is a common clinical finding increased considerably in recent years:

- ✓ frequent in **hospitalized patients**
- ✓ it can reach the **10% of positive urine cultures** in hospitals, intensive care units and tertiary care facilities
- ✓ major **risk factors** are indwelling urinary catheters, diabetes mellitus, use of broad-spectrum antibiotics, urinary obstruction
- ✓ ***C.* albicans** is the most commonly reported species in urine culture

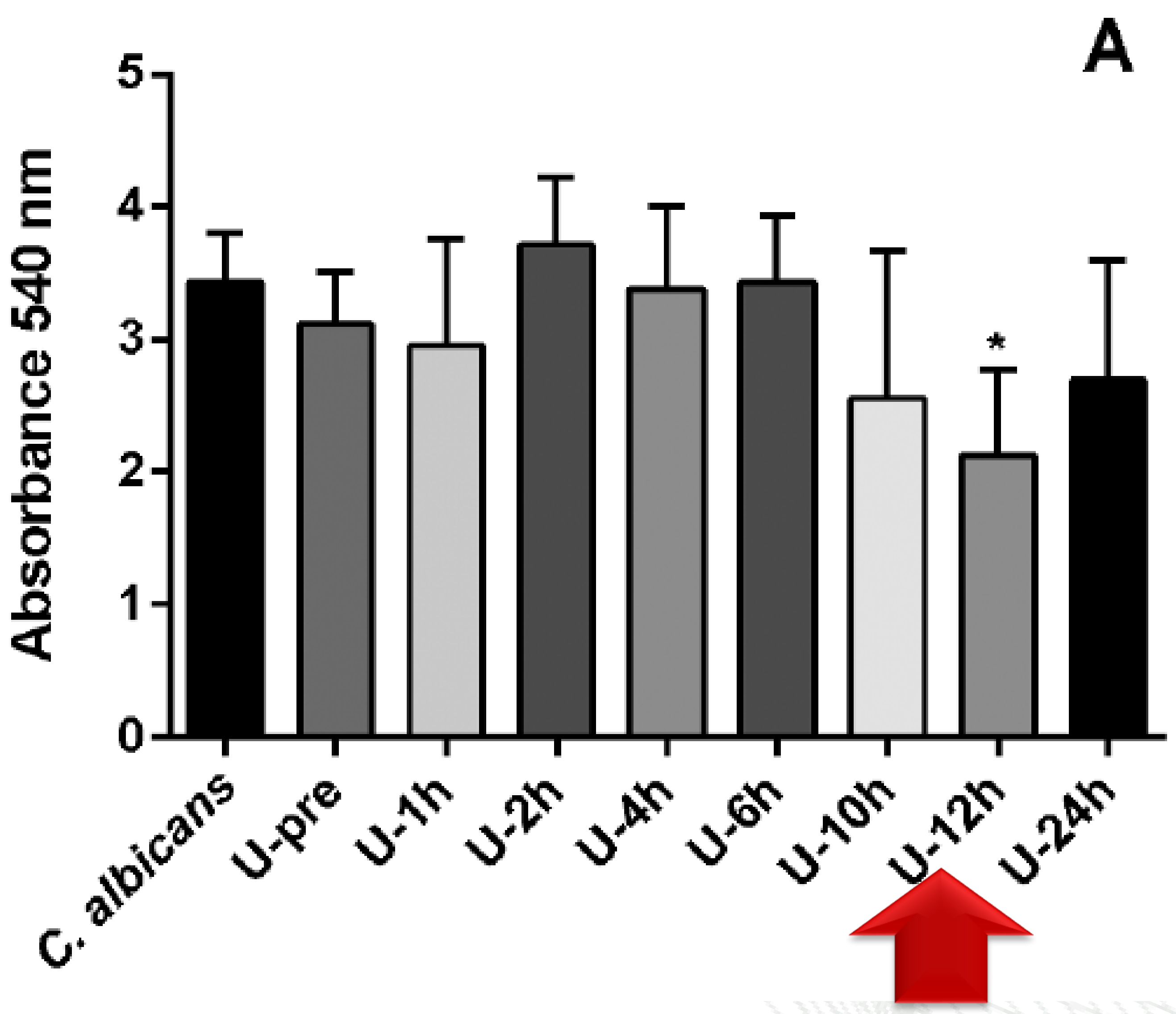
THE INCREASED RESISTANCE OF *CANDIDA* SPP. TO ANTIFUNGAL AGENTS (e.g. FLUCONAZOLE)
CALL FOR SAFE PREVENTIVE OR ADJUVANT INGREDIENTS AGAINST THE INFECTION


Lohse, M., et al. Nat Rev Microbiol 16, 19–31 (2018).
Gajdács, Márió, et al. Central European journal of urology 72.2 (2019): 209.
Fisher, John F. " Clinical infectious diseases 52.suppl_6 (2011): S429-S432.

# REDUCED *CANDIDA ALBICANS* ADHESION AND BIOFILM FORMATION

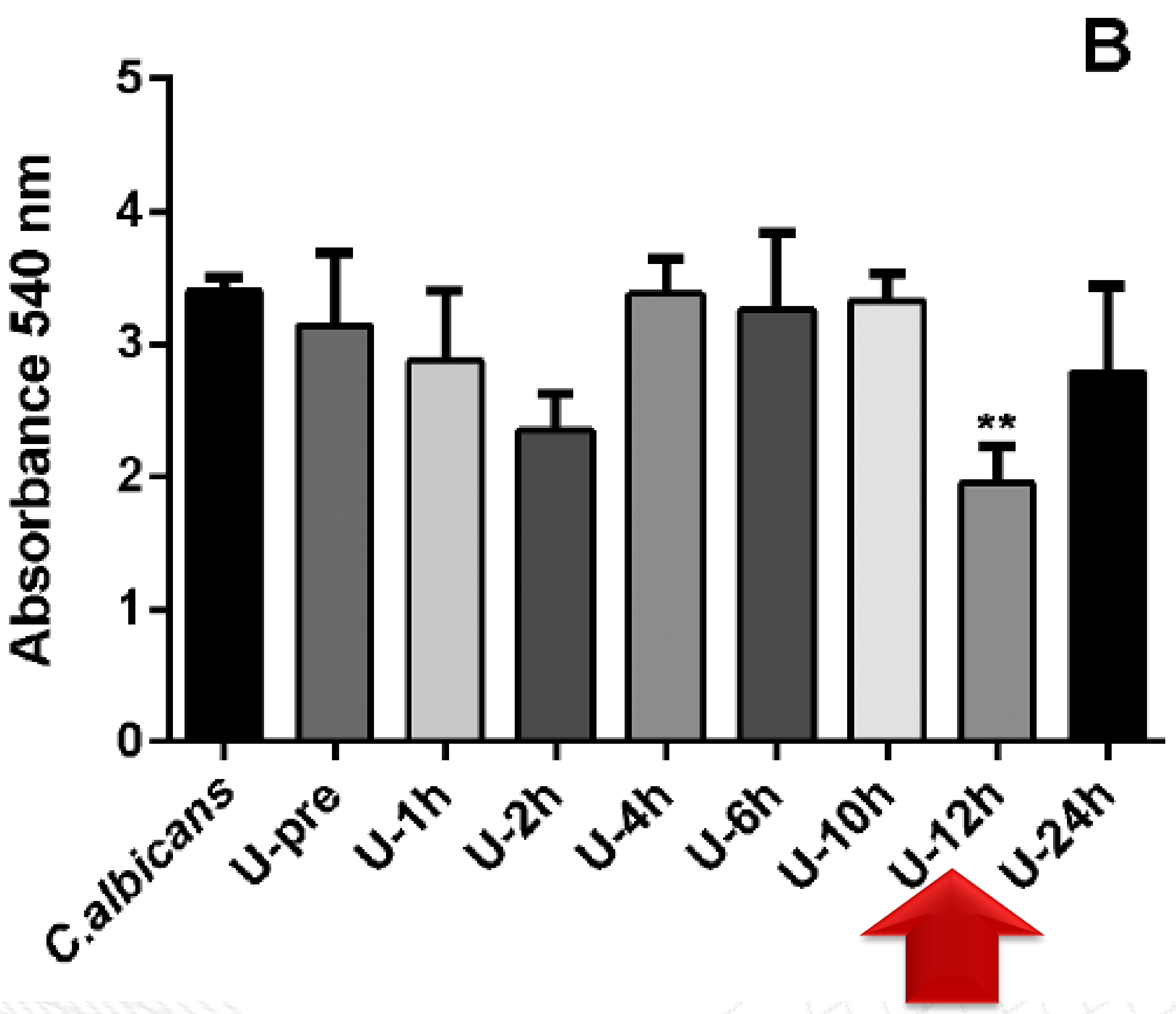
UNFORMULATED EXTRACT

PACs 36 mg/cps




ANTHOCRAN® phytosome

PACs 9 mg/cps




URINE COLLECTED AFTER 12h SHOW
THE HIGHEST *CANDIDA ALBICANS* INHIBITION

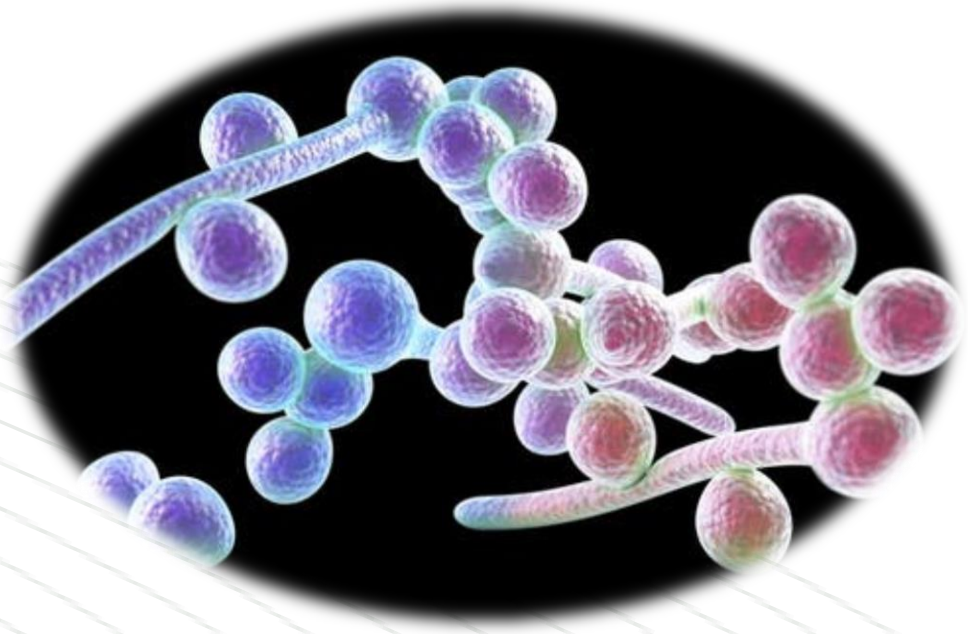
ANTHOCRAN® phytosome

WAS BIOEQUIVALENT TO UNFORMULATED CRANBERRY EXT. DESPITE THE MUCH LOWER UNITARY DOSE OF PACs (9 mg vs 36 mg).

*"GET THE SAME EFFECT WITH A LOWER CONTENT OF ACTIVE COMPOUNDS":*

*THE FAVOURABLE EFFECT OF PHYTOSOME® TECHNOLOGY ON PHYTOACTIVES ABSORPTION*

# REDUCED *CANDIDA ALBICANS* ADHESION AND BIOFILM FORMATION

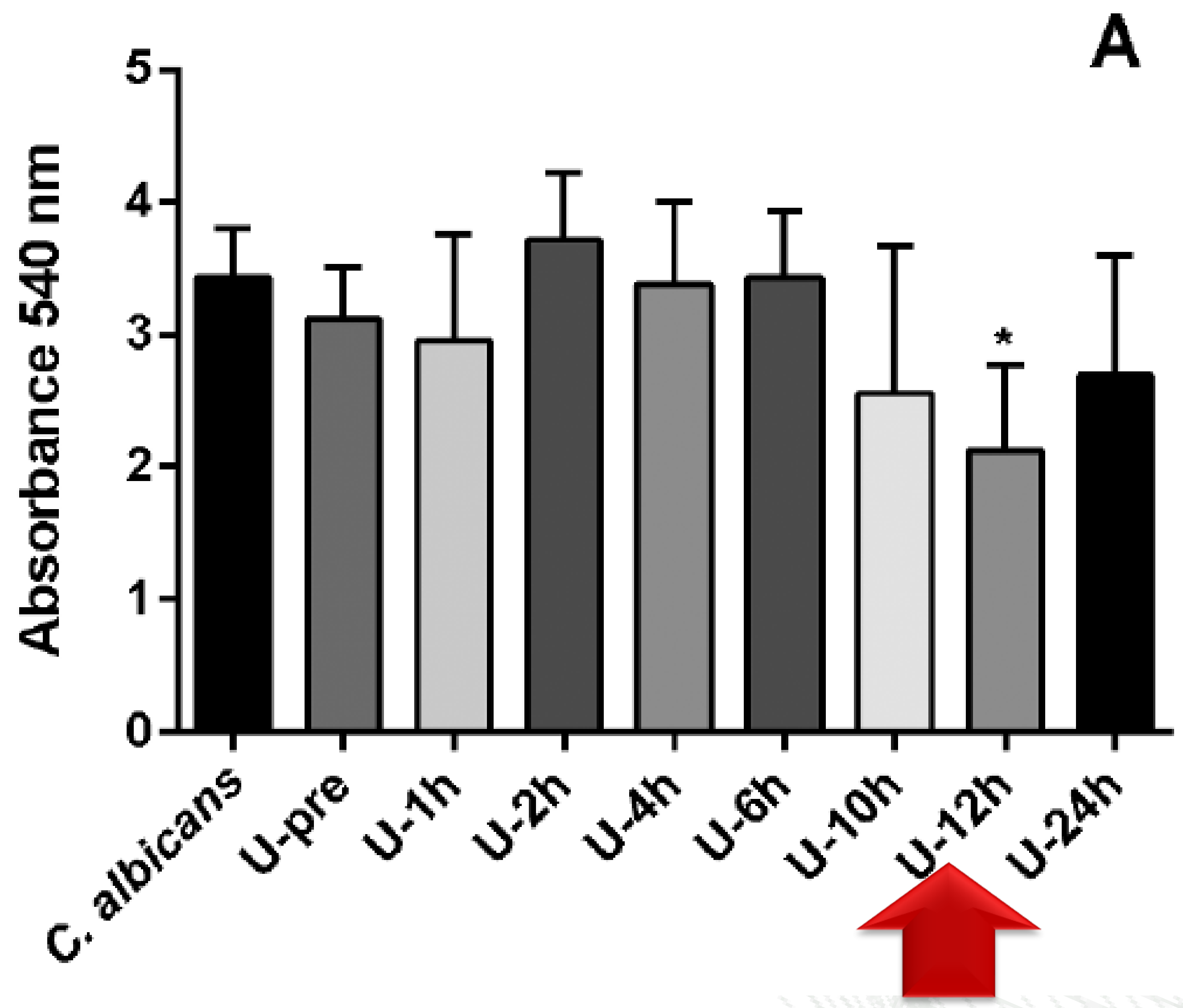


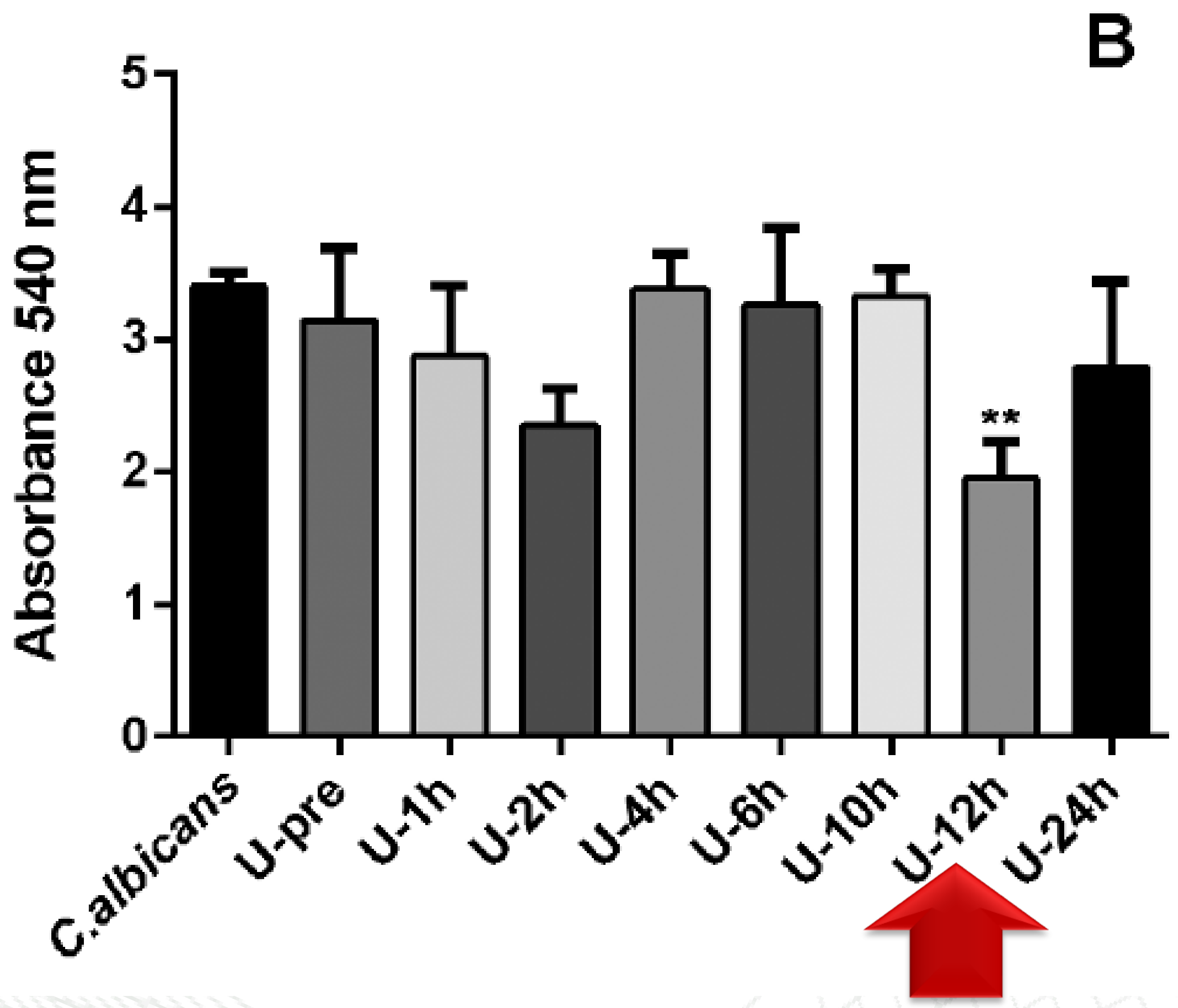
UNFORMULATED EXTRACT

PACs 36 mg/cps

ANTHOCRAN® phytosome

PACs 9 mg/cps




NEW

VALEROLACTONE DERIVATIVE

[5-(3′,4′-dihydroxyphenyl)-γ-valerolactone] was the most abundant metabolite in the most bioactive fraction (12h)

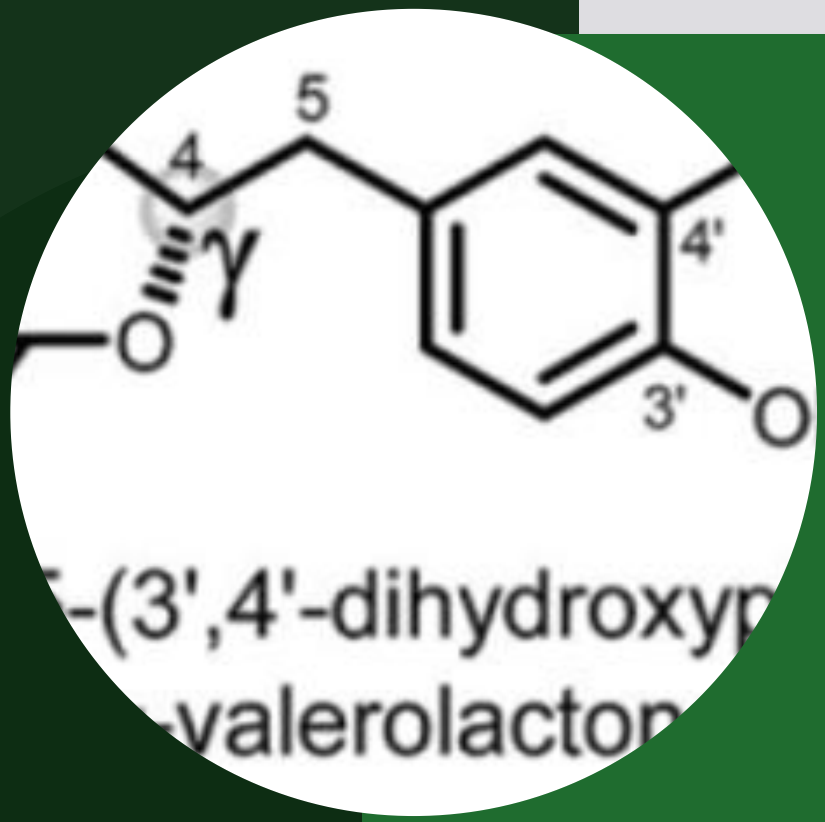
URINE COLLECTED AFTER 12h SHOW
THE HIGHEST *CANDIDA ALBICANS* BIOFILM INHIBITION

100 YEARS

# KEY MESSAGES FROM THE PK STUDY

ANTHOCRAN® phytosome

THE *IN VIVO* ACTIVITY OF CRANBERRY EXTRACTS CAN BE ASSOCIATED WITH THE <u>METABOLITES</u> OF PACS (e.g. valerolactones) RATHER THAN PACs, WHICH IS WHAT HAS BEEN ASSUMED SO FAR




NEW

#1 NEW COMPOUNDS (PA METABOLITES) HAVE BEEN IDENTIFIED IN HUMAN URINE

#2 *NEW* PACs METABOLITES ARE THE MOST ACTIVE AGAINST PATHOGENIC <u>ADHESION</u> (*Candida*)

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# HUMAN STUDY IN URINARY TRACT INFECTIONS (UTIs )

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# PROVEN EFFICACY IN PREVENTING UTIs

JOURNAL OF DIETARY SUPPLEMENTS
https://doi.org/10.1080/19390211.2021.1972074

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ARTICLE

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## Anthocran® Phytosome®: Prevention of Recurring Urinary Infections and Symptoms after Catheterization

Roberto Cotellese[a], Andrea Ledda[b], Gianni Belcaro[b,c], Maria R. Cesarone[b,c], Claudia Scipione[b], Valeria Scipione[b], Mark Dugall[b,c], Beatrice Feragalli[a], Antonella Riva[d], Pietro Allegrini[d], Giovanna Petrangolini[d] and Stefano Togni[d]

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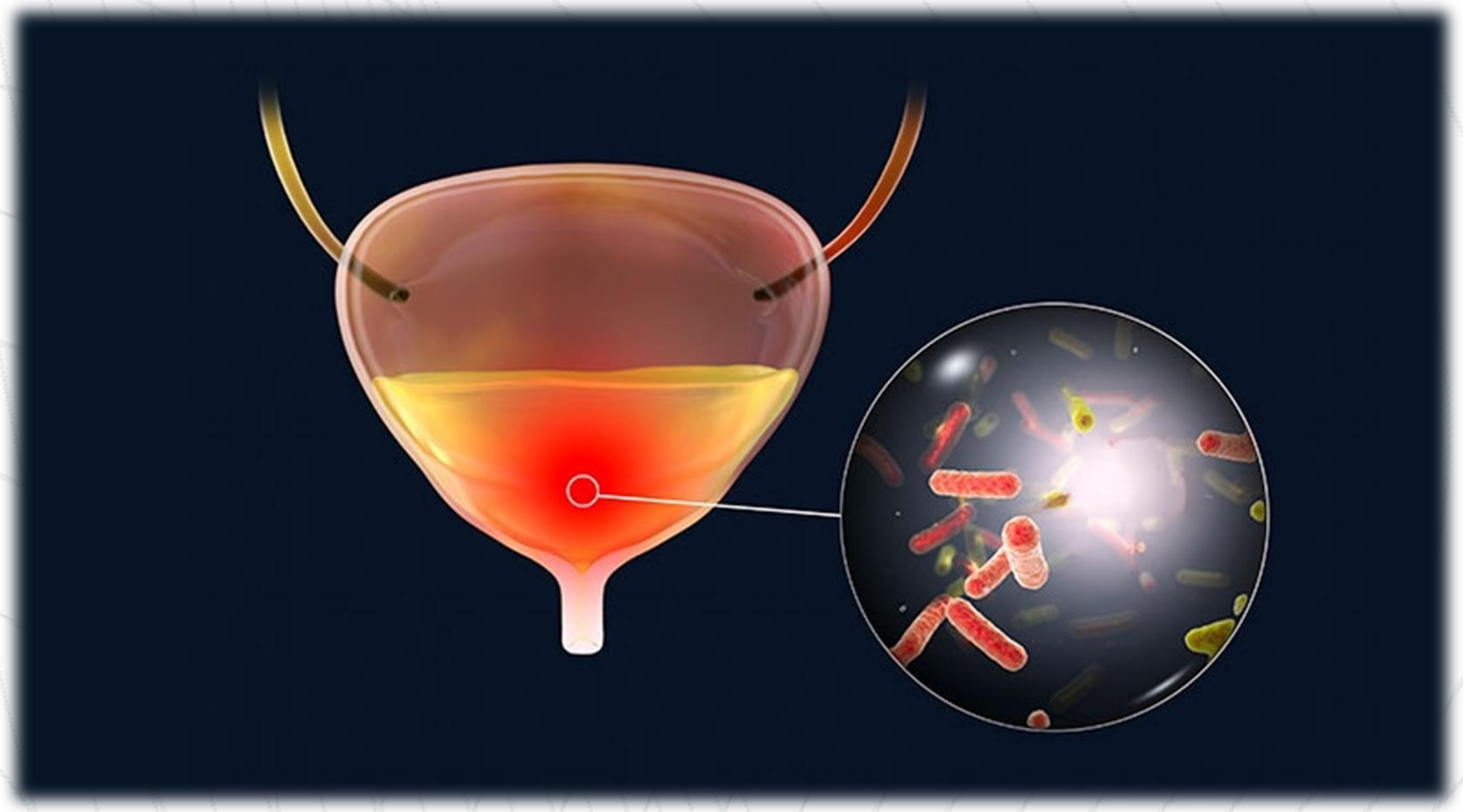
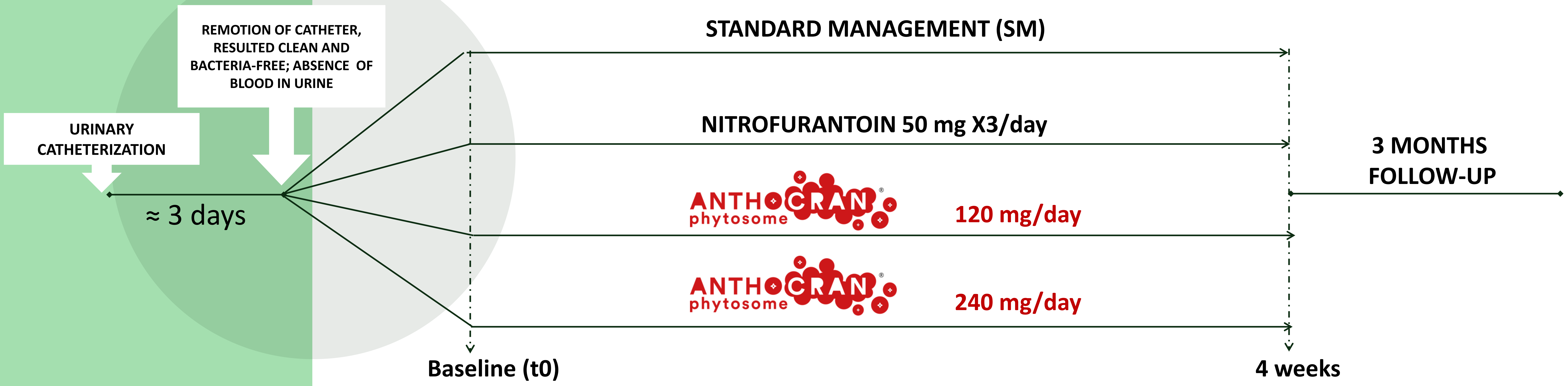


100 YEARS

Cotellese, Roberto, et al. "Anthocran® Phytosome®: Prevention of Recurring Urinary Infections and Symptoms after Catheterization." Journal of Dietary Supplements (2021): 1-13.

# STUDY DESIGN




**STUDY DESIGN:**

Open label, pilot, observational (registry)

**STUDY POPULATION:**

n. 64 otherwise healthy subjects (BMI<26, ≈50 years of age, 29 women) with non-complicated surgery requiring catheterization during post-operative period because of history of recurrent UTIs (R-UTIs) or risk for UTIs (= at least 2 symptomatic UTIs in the previous year or 1 episode of UTI in the previous month)

**STANDARD MANAGEMENT:**

Accurate hygiene (without local disinfectants); improved bladder care (drinking and voiding at appropriate time); reduced caffeine, spices and alcohol; careful hydration; mild exercise

**PRIMARY ENDPOINTS:**

❖ **Occurrence of urinary symptoms in the 4 weeks follow-up: frequency, dysuria, nacturia, urgency, pain**

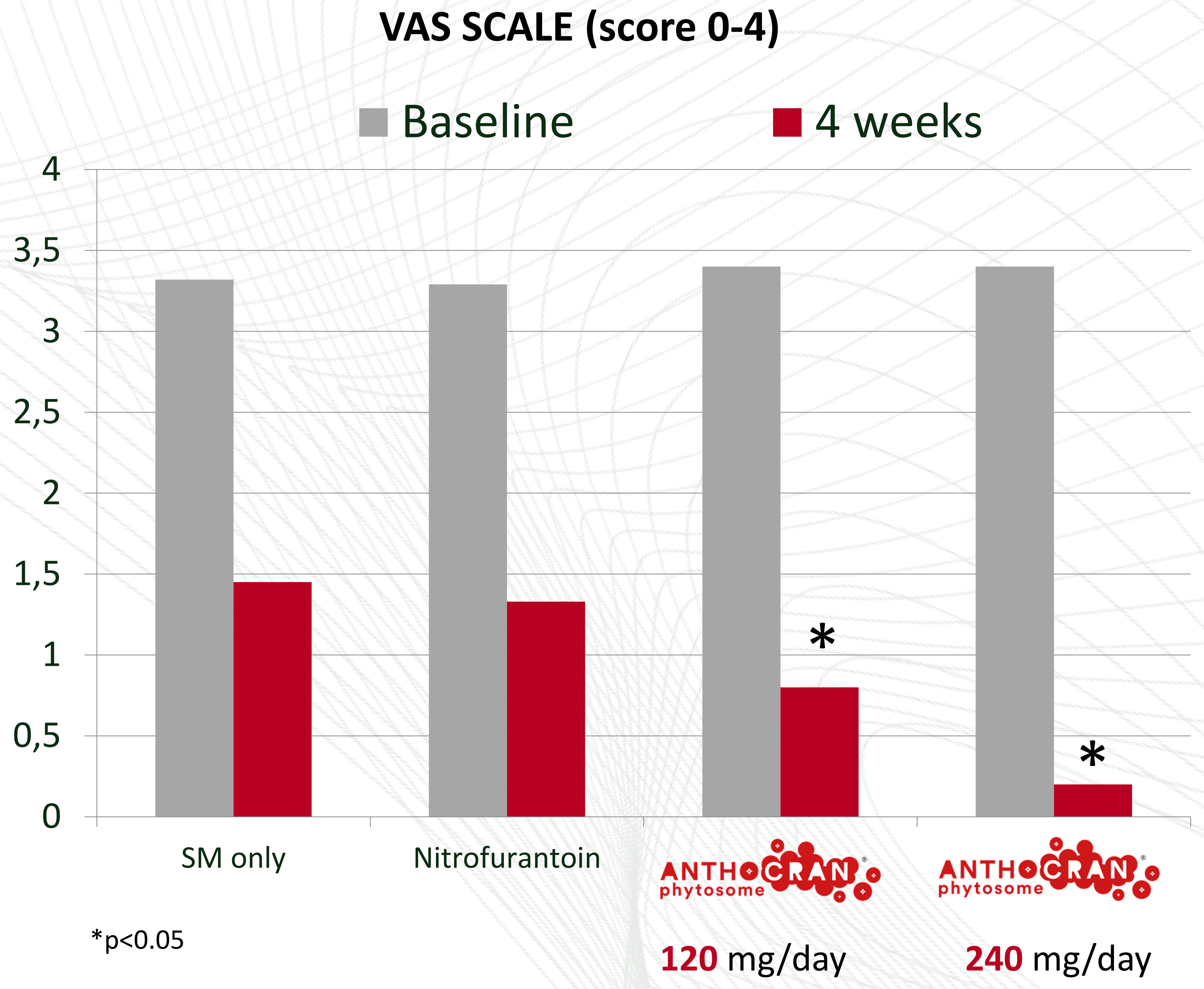
**SECONDARY ENDPOINTS:**

❖ Presence of increased bacterial charge in urine

❖ Visible presence of blood in urine

❖ Need for consultation and specialist’s evaluation

# EFFECTIVE IN REDUCING UTIs SYMPTOMS




*p<0.05

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**WAS SIGNIFICANTLY MORE EFFECTIVE IN REDUCING UTIs SIGNS AND SYMPTOMS, SHOWING A DOSE-RESPONSE:**

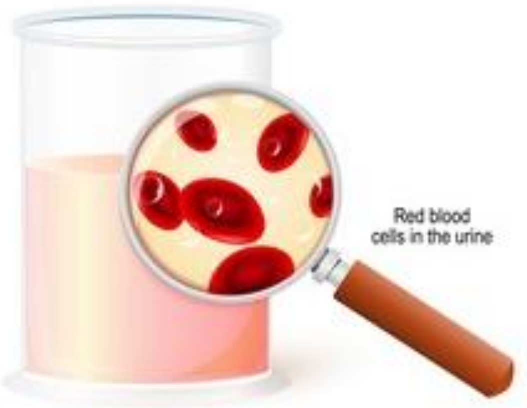
- ✓ Lower urinary frequency
- ✓ Lower urinary urgency
- ✓ Lower dysuria (=painful urination)
- ✓ Lower nocturia (=excessive urinating at night)
- ✓ Lower pain

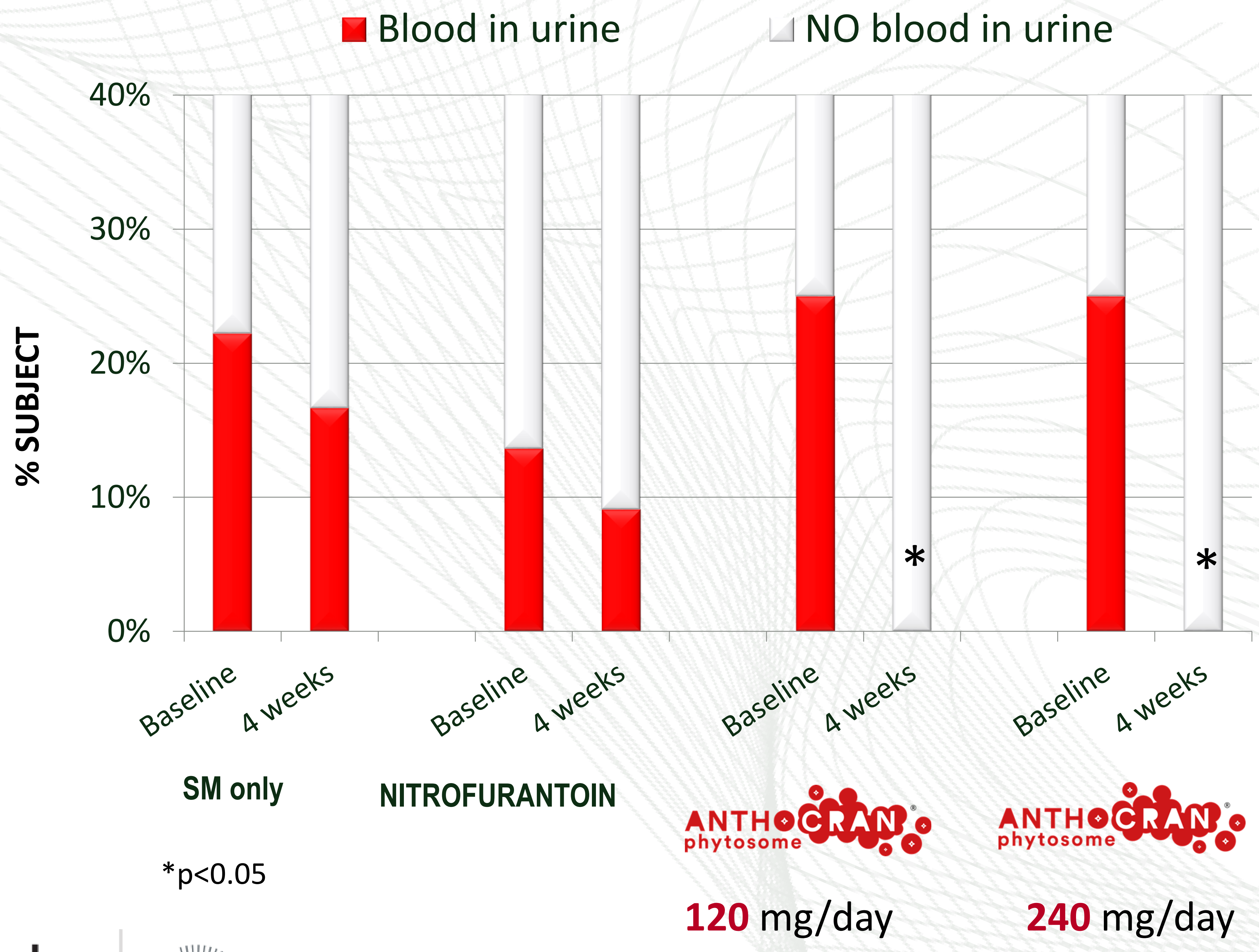


Cotellese, Roberto, et al. (2021)

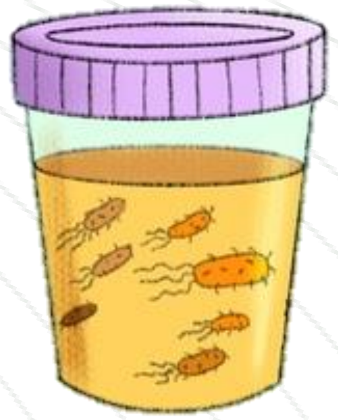
# ACHIEVED ZERO INDIVIDUALS WITH:

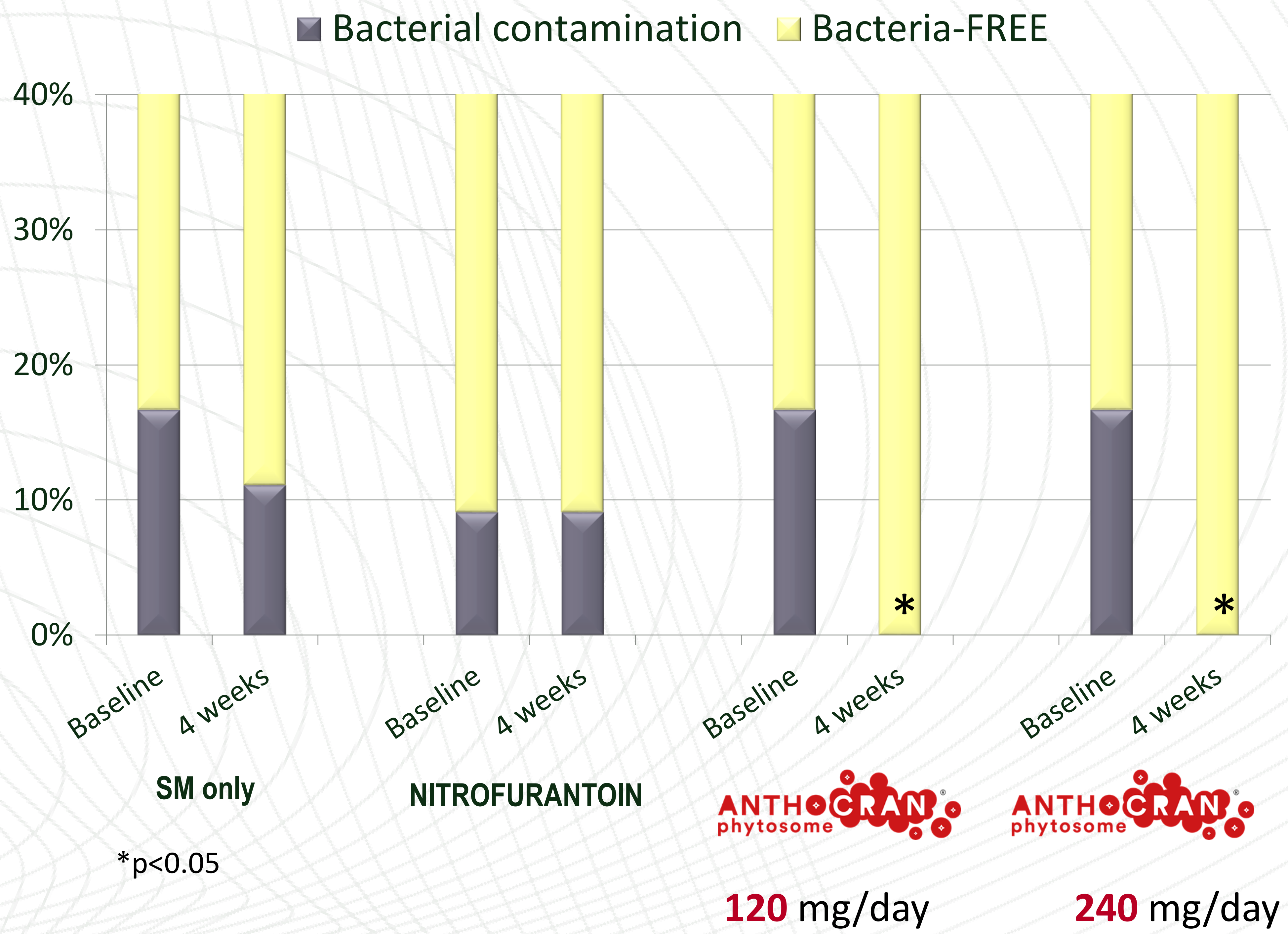
## HEMATURIA (blood in urines)




## URINES BACTERIAL CONTAMINATION






Cotellese, Roberto, et al. (2021)

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# EFFECTIVE PREVENTION OF RECURRENT UTIs

| TREATMENT | No. SUBJECTS WITH UTIs RE-OCCURRENCE IN THE 3 MONTHS FOLLOWING THE TREATMENT (no. / total subjects) |
|---|---|
| STANDARD MANAGEMENT only | 3/18 (17%) |
| NITROFURANTOIN 150 mg/day | 4/22 (18%) |
| ANTHOCRAN® phytosome 120 mg/day | **0/12 (0%)** |
| ANTHOCRAN® phytosome 240 mg/day | **0/12 (0%)** |

ANTHOCRAN® phytosome

**ACHIEVED ZERO SUBJECTS WITH RE-OCCURRENCE OF UTIs**

**IN THE 3 MONTHS FOLLOWING TREATMENT**

100 YEARS

Cotellese, Roberto, et al. (2021)


# TAKE HOME MESSAGES

- Exclusive Phytosome® technology optimizing phytoactives bioabsorption
- **Complete phytochemical profile investigation confirming the full polyphenols profile of natural cranberry**
- Deep investigation of human urine pharmacokinetics showing full polyphenolic profiles of cranberry phytoactives and metabolites
- **First report of PACs metabolites in human urine likely responsible of cranberry acknowledged health benefits**
- Clinical evidence in supporting urinary health and preventing recurrent UTIs
- **Superior clinical efficacy even with a lower content of PACs per unitary dose**
- Effective against pathogenic *Candida albicans* adhesion

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100 YEARS

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