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ORIGINAL RESEARCH

Urinary Excretion of Phenolic Acids by Infants and Children: A Randomised Double-Blind Clinical Assay

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Abstract

Objectives: The present study, which is part of the ISRCTN16968287 clinical assay, is aimed at determining the effects of cranberry syrup or trimethoprim treatment for UTI.

Methods: This Phase III randomised clinical trial was conducted at the San Cecilio Clinical Hospital (Granada, Spain) with a study population of 192 patients, aged between 1 month and 13 years. Criteria for inclusion were a background of recurrent UTI, associated or otherwise with vesico-ureteral reflux of any degree, or renal pelvic dilatation associated with urinary infection. Each child was randomly given 0.2 mL/Kg/day of either cranberry syrup or trimethoprim (8 mg/mL). The primary and secondary objectives, respectively, were to determine the risk of UTI and the levels of phenolic acids in urine associated with each intervention.

Results: With respect to UTI, the cranberry treatment was non-inferior to trimethoprim. Increased urinary excretion of ferulic acid was associated with a greater risk of UTI developing in infants aged under 1 year (RR 1.06; CI 95% 1.024–1.1; $P = 0.001$).

Conclusions: The results obtained show the excretion of ferulic acid is higher in infants aged under 1 year, giving rise to an increased risk of UTI, for both treatment options.

Keywords: phenolic acids, urinary infection, cranberry, ferulic acid, pediatric

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Introduction

Following reports that urinary tract infection (UTI) and vesico-ureteral reflux may be associated with different degrees of kidney damage,[1,2] the daily administration of low doses of antibiotics has been suggested as a possible treatment. Recent randomised, double-blind studies have shown that treatment with low doses of trimethoprim-sulfamethoxazole is associated with a modest decrease in the rate of symptomatic UTI in predisposed children.[2] However, prophylactic treatment with antibiotics does not completely eliminate the risk of new urinary infections; moreover, it affects the pathogens normally responsible for such infections and changes their patterns of resistance to antibiotics It is believed that 87% of all urinary infections are caused by *E. coli*, although *E. coli* is less common in children receiving antibiotic prophylaxis.[3] It has been reported that cranberry syrup outperforms a placebo treatment by up to 20% in preventing UTI among fertile age women.[4–6] A Cochrane review published in 2008[7] obtained similar results, although it concluded there was a need for more studies of good methodological quality.

Depending on age, gender and associated pathologies, the prevalence of UTI among children may range from 2% to 8%. Except in the first 2 months of life, when infection may be secondary to haematogenous dissemination, UTI is caused by an ascending mechanism in the urinary tract, mainly due to gram-negative bacteria. The adhesion of uropathogenic *E. coli* is a process that takes place prior to the development of infection, when the exposed lectins on the bacteria surface adhere to carbohydrates from the epithelium. The components of cranberry syrup are known to inhibit the adherence of *E. coli* to the epithelial cells, both in vivo[8] and in vitro,[9] and this inhibition seems to be produced by a non-dialysable component, namely the A-type proanthocyanidin present at high concentrations in cranberry syrup.[10]

Cranberries also contain significant quantities of polyphenols such as flavonoids, isoflavonoids, coumarins and anthocyanins. Polyphenols are an important component of the diet, although they are not necessarily very active in the organism, due to a low level of intrinsic activity, or because they are poorly absorbed in the intestines, are metabolised or are eliminated rapidly. Most polyphenols are present in foods in the form of esters, glycosides or polymers which cannot be absorbed in their native form and must be hydrolysed by the intestinal enzymes or by colonic microflora in order to be absorbed.[11]

The present study forms part of the ISRCTN16968287 clinical assay. Our primary objective was to determine the risk of UTI associated with cranberry or trimethoprim treatment, while the secondary objective was to determine the levels of phenolic acids in urine associated with each intervention.

Methods

Study participants

From January 2009 to October 2010, children aged from 1 month to 13 years and treated at the paediatric nephrology and urology departments in our hospital were considered for this study. Criteria for inclusion were a background of recurrent UTI (more than 2 episodes of infection in the last 6 months), associated or otherwise with vesico-ureteral reflux of any degree, or renal pelvic dilatation associated with urinary infection. The presence of infection was confirmed by urine culture (>100,000 CFU/mL) using a "mid-stream" urine sample or a urine collection bag, after asepsis of the urethral meatus with chlorhexidine, or >10,000 CFU/mL if a catheter specimen of urine was obtained. In both cases, the presence or otherwise of a urine sediment with >20 leucocytes per field was determined. The test endpoint was the presence of urinary infection. Criteria for exclusion were the co-existence of UTI with other infectious diseases or with metabolic diseases, chronic renal insufficiency, the presence of allergy or intolerance to any of the components of cranberry syrup or trimethoprim, the existence of blood dyscrasia or the express wish of the parent or guardian to exclude the child from the study. This study was approved by the local ethics committee, and in all cases the parents or guardians gave their written informed consent.

Study design and intervention

The study was designed as a Phase III randomised clinical trial, with the treatment option concealed from both patients and researchers. There were two treatment branches: cranberry syrup and trimethoprim. Both groups received a single daily dose of 0.2 mL/kg of syrup at 8.00 p.m. The patients who were given trimethoprim received a concentration of 8 mg/mL, and it was masked with cochineal red dye (E-124)

and packaged in opaque tubes. Study subjects were randomised in permuted blocks of 5 using appropriate software.

Characterization of cranberry syrup

The cranberry syrup (Pharmatoka Lab., France) was characterised at the Department of Analytical Chemistry, Faculty of Sciences, University of Granada,[12] and provided as a dispersion of 2.8% cranberry extract Gykacran® in glucose syrup. The composition of the cranberry syrup, with respect to its different polyphenol fractions, has been published previously.[12] The concentration of phenolic acids in the syrup is shown in Table 1. The total amount of phenolic acids was 454 µg/mL.

Determination of phenolic acids

Levels of phenolic acid in urine were determined in urine samples from 93 randomly-chosen patients from the ISRCTN16968287 clinical assay, at the Institute of Public Health and Clinical Nutrition, Kuopio, Finland. The following phenolic acids, with diverse benzoic, acetic, propionic and cinnamic acid derivatives, were analysed; *p*-hydroxybenzoic, protocatechuic, vanillic, syringic, gallic, 3,4-dihydroxyphenylacetic, *m*-hydroxyphenylacetic, homovanillic, 3,4-dihydroxyphenylpropionic, *m*-hydroxyphenylpropionic, dihydroferulic, dihydroisoferulic, caffeic, ferulic, sinapinic, isoferulic, *p*-coumaric and *m*-coumaric acids. These compounds cover a wide range of metabolites and dietary phenolic acids; they constitute a fragmentation product of procyanidins,[13,14] and were measured to evaluate fragmentation into other phenolic metabolites. Analysis of phenolic acids also provides information about the fragmentation of flavonols and catechins.[15,16] The phenolic acids in the cranberry syrup samples were first hydrolysed with enzymes (obtained from Helix Pomatia) and then with sodium hydroxide.

Table 1. Phenolic acids in cranberry syrup.

Phenolic acid	nMol/mL
Protocatechuic acid	133.5
Vanillic acid	342.7
Chlorogenic acid	411.5
Chlorogenic acid converted to caffeic acid	411.5
Caffeic acid	18.7
p-coumaric acid	1789.2
Ferulic acid	23.1

Sample size and statistical analysis

There is assumed to be a 20% risk of recurrence of UTI during the first year of antibiotic treatment. The present study is a non-inferiority clinical trial, in which it is hypothesised that cranberry syrup treatment is equivalent (non inferior) to trimethoprim. The limits of equivalence were established at ±10%, with an alpha error of 5% and the power of the study, 80%. In accordance with these data, the sample size was calculated to be 109 patients per group.

The inter-group comparison of urinary polyphenol excretion was performed using the following tests: *t*-test for independent samples; linear regression analysis for the concentrations of the different polyphenolic components of the cranberry syrup and in the urinary phenolic acids; Cox's regression analysis for the risk of UTI and the different polyphenolic acids excreted in the urine, as recorded during follow-up.

Results

The study began on 1 January 2009 and ended on 31 October 2010 (curtailed by the lack of financial resources for its continuation). The maximum follow-up period of each patient recruited was one year. Due to problems in medical practice during the randomisation process, 75 patients received cranberry syrup and 117 received trimethoprim. 6 patients were lost to the study (3 in each group). Among the study population, 82 infants were aged less than one year. 51 of these were treated with trimethoprim and 31 with cranberry syrup. The prevalence of UTI associated with trimethoprim prophylaxis was 21%, versus 32% for those given the cranberry syrup (LogRank 1.13; $P = 0.28$). Of the 49 children aged from 1–3 years, 28 were treated with trimethoprim and 21 received cranberry syrup. Among these children, the prevalence of UTI associated with trimethoprim prophylaxis was 14.2%, versus 4.7% for those given the cranberry syrup (LogRank 1.29; $P = 0.25$). Of the 55 children aged over 3 years, 34 were given trimethoprim, and 21 received cranberry syrup. Among these children, the prevalence of UTI associated with trimethoprim prophylaxis was 38%, versus 38% for those given the cranberry syrup (LogRank 0.08; $P = 0.77$).

Mean urinary osmolarity in lactating infants aged under 1 year was 356 mOsm/L (SD 233); in the children aged 1–3 years, the corresponding value was 725 mOsm/L (SD 199), while among the children

Table 2. Urinary excretion of phenolic acids of dietary origin by age strata.

(µMol/g creatinin)	Under 1 year			1–3 years			Over 3 years			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Protocatechuic acid	37	5.2	4.8	27	3.1	2.0	29	3.2	3.0	93	4.0	3.7
Syringic acid	37	0.5	0.8	27	1.0	1.9	29	1.2	2.3	93	0.8	1.7
Caffeic acid	37	1.3	3.6	27	0.5	1.1	29	0.8	1.3	93	0.9	2.5
p-coumaric acid	37	0.8	1.5	27	1.4	4.8	29	0.7	1.3	93	1.0	2.8
Ferulic acid	37	15.6	16.9	27	6.6	9.4	29	6.0	4.3	93	10.0	12.3
Sinapinic acid	37	0.0	0.0	27	0.0	0.0	29	11.0	4.7	93	0.3	2.6
Total dietary phenolic acids	37	23.4	20.8	27	12.5	18.0	29	12.9	10.8	93	17.0	18.0

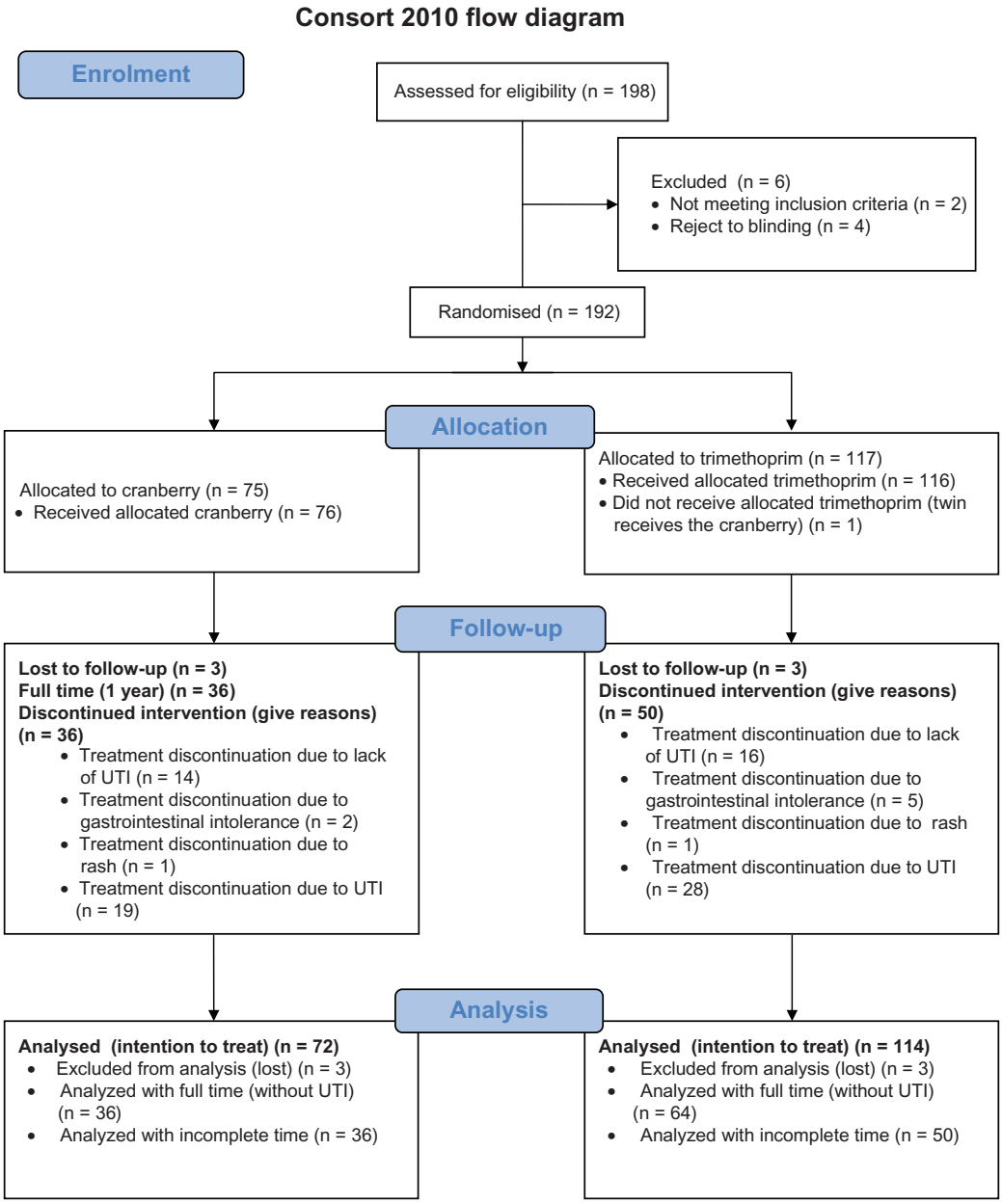

Figure 1. Flow diagram.

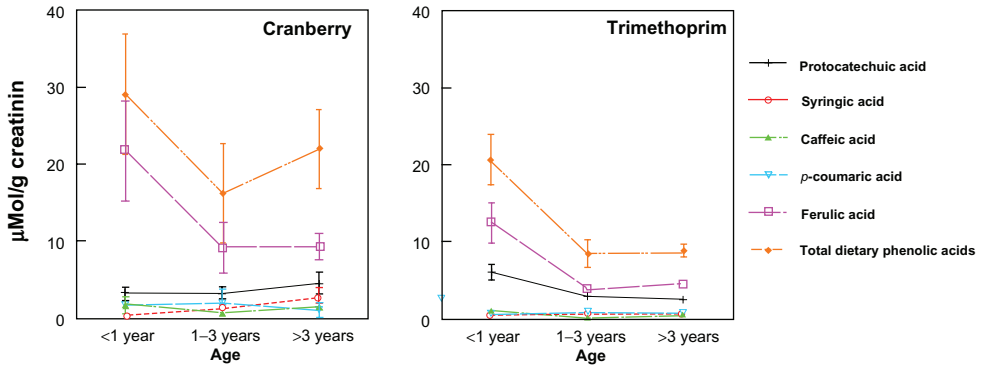

Figure 2. Urinary excretion of dietary phenolic acids following the intake of cranberry syrup or trimethoprim as a treatment for recurrent urinary infection.
Note: Mean values (SEM) are shown.

aged over 3 years, it was 738 mOsm/L (SD 254). Thus, osmolarity among the lactating infants aged less than 1 year was significantly lower than that observed in the older age groups. No significant differences were detected in this respect between children who developed UTI and those who did not, and therefore, *a priori*, we discount the greater or lesser intake of water as an element associated with the development of UTI. In our sample, 44.3% of the urinary infections affected subjects aged less than one year, with 26.5% affecting those aged 1–3 years, and 29.2% affecting those aged over three years.

Analysis of urinary excretion of dietary phenolic acids

At 12 hours after receiving the cranberry syrup, these patients eliminated slightly greater urinary concentrations of total phenolic acids than did the patients who received trimethoprim (22.2 µMol/g creatinine (SD 23.4), vs. 13.9 µMol/g creatinine (SD 13.2); t = 2.18, $P = 0.03$, respectively). We compared the quantity of cranberry syrup consumed with the urinary excretion of ferulic acid, and found no statistically significant association (b = –3.3; t = 1.8; $P = 0.08$). The urinary excretion of ferulic acid and of total phenolic acids was higher among the infants aged under 1 year, with no significant differences in this respect being observed between those given cranberry syrup or trimethoprim. Moreover, the patients who developed urinary infection during the follow-up period had higher urinary levels of ferulic acid than did those who completed the follow-up period without any such infection (t = 2.39; $P = 0.01$) (Fig. 3).

In general, increased urinary osmolarity was associated with a lower excretion of ferulic acid, with creatinine decreasing by 0.016 µMol/g for each increase of 1 mOsm/L in urinary osmolarity (b = 0.016; $P < 0.001$).

After performing Cox's regression analysis on the ferulic acid and adjusting for urinary osmolarity, we observed that increased urinary excretion of

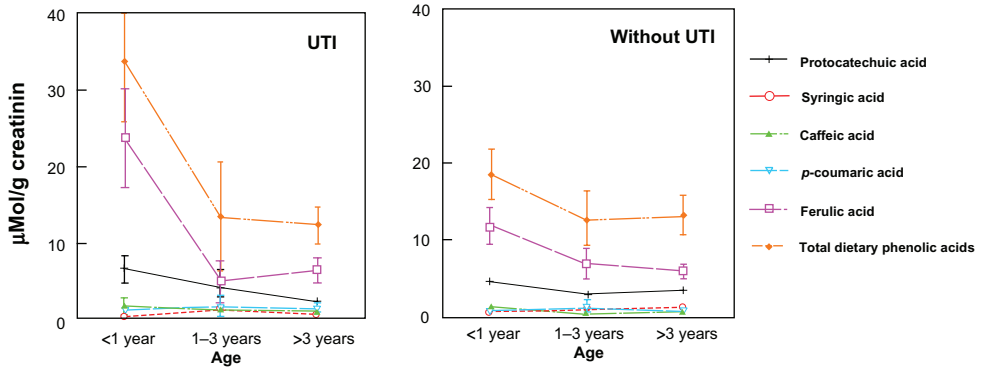

Figure 3. Urinary excretion of dietary phenolic acids in patients who subsequently developed UTI and in patients who did not.
Note: Mean values (SEM) are shown.

ferulic acid was associated with a greater risk of UTI developing in infants aged under 1 year (RR 1.06; CI 95% 1.024–1.1; $P = 0.001$). As the prevalence of UTI was greater among the infants aged under 1 year, we adjusted the Cox's regression for urinary osmolarity and age, thus obtaining a relative risk for UTI of 1.04 (CI 95% 1.02–1.08). In the children aged 1–3 years and over three years, the relative risk of UTI associated with increased ferulic acid was 0.97 (CI 95% 0.79–1.27; $P = 0.96$) and 1.01 (CI 95% 0.86–1.19; $P = 0.88$), respectively.

Analysis of urinary excretion of metabolic phenolic acids

The urinary excretion of total phenolic acids of metabolic origin among the patients given cranberry syrup was 681.5 µMol/g creatinine (SD 573.2), versus 664.6 µMol/g creatinine (SD 656.4) for those given trimethoprim. In the children aged under 1 year, the urinary excretion of homovanillic acid was significantly greater among those given cranberry syrup ($t = 2.49$; $P = 0.01$); this difference was not observed in the other age groups (Table 3).

Only among the children aged over 3 years did we observe levels of 4-hydroxybenzoic acid that were significantly greater among the children who developed a urinary infection. Cox's regression analysis did not reveal any change in the risk of UTI associated with a greater excretion of phenolic acids of metabolic origin.

Discussion

The excretion of ferulic and homovanillic acids was greater among the infants aged less than 1 year than in the other age groups. These infants presented a greater frequency of UTI, which was significantly related to the greater excretion of ferulic acid. The increased excretion of homovanillic acid during treatment with cranberry syrup could be of interest with respect to designing studies such as the determination of catecholamines and their metabolites in children with possible neuroblastomas or pheochromocytomas. This aspect has been discussed by Combet et al.[17] Other authors have observed that a diet of cereals supplemented with berries can cause an increase in the urinary excretion of homovanillic acid.[18] Ferulic acid is the phenolic acid that is most abundantly excreted in the urine when a cereal diet is consumed.[11] Nevertheless, the strong association observed between the excretion of ferulic acid and the risk of urinary infection requires further investigation. Ferulic acid has presented

Table 3. Urinary excretion of phenolic acids of metabolic origin by age strata.

(µMol/g creatinin)	Under 1 year			1–3 years			Over 3 years			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
3-coumaric acid	37	0.0	0.0	27	0.0	0.0	28	0.0	0.0	92	0.0	0.0
Isoferulic acid	37	5.0	7.7	27	1.4	1.7	28	2.9	3.8	92	3.3	5.6
Dihydroferulic acid	36	5.0	6.7	27	6.2	12.4	28	3.5	3.9	91	4.9	8.2
3,4-di-dihydroxy phenylpropionic acid	37	4.2	6.6	27	2.1	2.2	28	2.1	2.5	92	2.9	4.6
m-hydroxyphenyl propionic acid	37	1.8	4.3	27	5.1	18.4	28	2.3	3.3	92	2.9	10.5
p-hydroxyphenyl propionic acid	37	0.1	0.2	27	3.7	14.5	28	0.0	0.1	92	1.1	7.9
Homovanillic acid	37	116.4	39.1	27	75.7	36.8	28	50.3	22.7	92	84.4	44.1
3,4-di-hydroxyphenyl acetic acid	37	32.4	20.9	27	22.1	17.5	28	16.6	8.0	92	24.6	18.0
3-hydroxyphenyl acetic acid	37	16.1	21.3	27	48.6	55.2	28	27.3	34.2	92	29.02	39.7
4-hydroxyphenyl acetic acid	37	488.7	393	27	253.8	324	28	154.3	57.0	92	318.0	337
Vanillic acid	37	252.3	529	27	145.6	176	28	80.5	111	92	168.7	359
3-hydroxybenzoic acid	37	0.5	1.9	27	1.9	6.5	28	0.4	1.5	92	0.9	3.8
4-hydroxybenzoic acid	37	40.9	30.7	27	37.9	55.7	28	19.8	11.9	92	33.6	37.2
Total metabolic phenolic acids	37	963.1	730	27	593.6	594	28	359.7	181	92	671.0	622

in vitro activity as an inhibitor of interleukin 8,[19] with a pro-inflammatory and neutrophil activating effect. In consequence, various forms of traditional medicine have used the rhizome of *Cimicifuga* sp., which contains high concentrations of ferulic and isoferulic acid, as a remedy for various inflammatory processes.[20] It seems reasonable to believe that persistent high concentrations of ferulic acid in the urine could favour the development of urinary infections, by inhibiting the host's pro-inflammatory mechanisms.

Cranberry syrup has been found useful for treating UTI in adults[5,7] and children.[21] Various studies have related the bioactivity of cranberry with its content of proanthocyanidins.[9,22] Lavigne et al[23] observed that the anti-adherent effect of cranberry is dose-dependent, and therefore the concentration of proanthocyanidins in urine determines the anti-adherent effect and, thus, clinical efficacy. In our study, due to the lack of references to comparable studies of a paediatric population, we considered the cranberry dose recommended for adults and adjusted it according to body mass. As the determination of proanthocyanidins in urine presents results that are at the limits of sensitivity for the measuring equipment used, and as the concentrations of phenolic acids in urine are equivalent for most fractions in patients given either cranberry or trimethoprim, we believe that the doses of cranberry syrup used in this study might be insufficient for the lowest-weight infants. This age group, with urinary excretion featuring high levels of ferulic acid, should be given a fixed amount of cranberry syrup in order to ensure a minimum concentration of proanthocyanidins in the urine. The cranberry syrup used in this study was characterised and found to contain different concentrations of flavonoids, flavonols, proanthocyanidins and low concentrations of ferulic acid.[12] Therefore, we believe the high levels of ferulic acid detected in infants aged less than 1 year were probably due to their higher dietary intake of cereals. Although some of these compounds, and particularly the glycoside flavonoids, may be absorbed in the small intestine and eliminated in the urine,[24] it is accepted that while various hydroxycinnamic acids are subject to cellular metabolic metabolism, most of the polyphenolic compounds are broken down by intestinal microflora in the colon. Up to 44% of the protocatechuic acid is derived from the anthocyanins consumed, especially the cyanidin-3-glucoside.[25] Dietary flavonols and especially quercetin could be metabolised, mainly into phloroglucinol and 3,4-dihydroxyphenylacetic acid.[26] The procyanidins in the diet are metabolised by the intestinal microflora, fundamentally into 3,4-di-dihydroxyp henylpropionic, protocatechuic, 4-hydroxybenzoic and 3,4-dihydroxyphenylacetic acids, which are eliminated in the urine.[27] In our study, the patients who were given cranberry syrup presented a urinary excretion of 3,4-di-dihydroxyphenylpropionic, protocatechuic and 3,4-dihydroxyphenylacetic acids which was similar to that of the patients given trimethoprim. It is noteworthy that the children aged over 3 years who developed UTI presented higher urinary concentrations of 4-hydroxybenzoic acid, which could indicate a greater metabolism by the intestinal microflora of the proanthocyanidins supplemented with the syrup.

According to the results obtained, the excretion of ferulic acid is higher in infants aged under 1 year. This is assumed to be related to the predominance of cereals in the diet and not to the ingestion of cranberry or trimethoprim. However, as we did not conduct a nutritional survey and due to problems in the randomization process, we cannot be categorical in this respect. This increased excretion of ferulic acid was associated with an increased risk of urinary infection.

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Competing Interests
Author(s) disclose no potential conflicts of interest.

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Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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