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ORIGINAL ARTICLE

The influence of dietary supplementation with cranberry tablets on the urinary risk factors for nephrolithiasis

Elaine J. Redmond[1] · C. F. Murphy[1] · J. Leonard[1] · K. Faulds[1] · S. Abdelfadil[1] · V. E. Crowley[1] · T. H. Lynch[1] · R. P. Manecksha[1]

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Abstract

Purpose Cranberry supplements are commonly used as a natural deterrent to urinary tract infection. However, one small study ($n=5$) which showed an increase in urinary oxalate levels following cranberry supplementation has led to its use with caution among patients susceptible to nephrolithiasis. Furthermore, most commonly available cranberry tablet preparations contain vitamin C, which has been independently shown to increase urinary oxalate excretion. The aim of this study is to investigate the influence of cranberry supplementation on urinary oxalate excretion.

Methods Fifteen participants were randomised to receive cranberry tablets alone or cranberry tablets containing vitamin C. Tablets were taken at the manufacturers recommended dosage for a period of 14 days. Participants provided a 24 h urine collection at trial entry and day 14. Urinary variables were compared to assess for changes in oxalate levels.

Results The median age was 27 years (21–43). There was no difference in the 24 h urine volume pre or post commencement of cranberry tablets (1.7 vs 2 L, $p=0.07$). An increase in median urinary oxalate excretion was observed in participants taking both cranberry-only tablets (0.10 mmol/day) and tablets containing vitamin C (1.15 mmol/day).

Conclusion Dietary supplementation with cranberry increases urinary oxalate excretion and should be avoided in patients at risk of urolithiasis.

Keywords Cranberry · Urolithiasis · Oxalate · Vitamin C

Introduction

Cranberry is an evergreen shrub native to North America. The distinctive berries were historically used by Native Americans both as a food source and a natural deterrent to bladder and kidney diseases [1]. Early studies from the 1920s attributed the medicinal properties of the berries to their high acid content [2]. Later research identified that the high concentration of anthocyanidins can inhibit adherence of bacteria to the bladder urothelium, thus reducing the risk of infection [3, 4]. Although the efficacy of cranberry supplementation has been questioned in the past, its use has recently fallen back in favour following the publication of a meta-analysis reporting significant evidence for its use in the prevention of urinary tract infection [5].

The National Center for Complementary and Integrative Health (NCCIH) has advised the use of cranberry with caution in individuals at risk of urolithiasis [6]. This recommendation comes based on a small study ($n=5$) which showed an increase in oxalate excretion following cranberry supplementation. However, although most physicians will be conscious of the interaction between cranberry and anticoagulants [6], the safety profile in relation to renal stone formation does not appear to be as widely acknowledged within the medical community. Furthermore, the majority of commercially available cranberry tablets are fortified with vitamin C, which has been independently shown to increase urinary oxalate excretion in a number of studies [7–12].

The aim of this study was to investigate the effect of cranberry supplementation, with and without vitamin C, on 24 h urinary oxalate excretion.

✉ Elaine J. Redmond
elaineredmond@rcsi.ie

[1] Department of Urology, St. James's Hospital, Dublin 8, Ireland

Methods

Eighteen adult volunteers (ten male, eight female) were recruited for the study by open advertisement. Exclusion criteria included history of renal stones, liver disease, anticoagulation and calcium/vitamin supplementation. Due to the potential confounding effect of ascorbic acid, participants were randomly allocated 1:1 to receive cranberry tablets alone or cranberry tablets containing vitamin C. Tablets were taken at the manufacturers recommended dosage for a period of 14 days. Group 1 received tablets containing a daily dose equivalent to 32.4 g of fresh cranberries (13.5 mg anthocyanidins). Group 2 received tablets containing a daily dose equivalent to 12.6 g of fresh cranberries and 20 mg of vitamin C (anthocyanidin dose not specified). A 24 h urine collection was obtained from each participant at trial entry and day 14 for determination of calcium, oxalate, sodium, potassium, urea, creatinine, magnesium, uric acid and citrate. Samples were collected in a plain container without preservatives which was acidified immediately on delivery to the laboratory. The sample was then heated to 60° to return the oxalate to solution. This method of delayed addition of acid preservative simplifies the collection process and decreases the risk of injury to the patient from the extremely corrosive acid. This method does not affect the biochemical parameters of the urine constituents [13]. Urinary oxalate levels were determined using an enzymatic spectrophotometric method based on the oxidation of oxalate by oxalate oxidase followed by measurement of hydrogen peroxide (H_2O_2) produced during the reaction by a peroxidase-catalysed reaction. Urinary variables were compared to assess for changes in oxalate levels following supplementation. Calcium, oxalate, magnesium and citrate data were used to evaluate the risk of calcium oxalate crystallisation by calculating the Tiselius index using the following formula: $1.9 \times \mathrm{Ca}(0.84) \times \mathrm{Ox} \times \mathrm{Mg}\text{-}(0.12) \times \mathrm{Cit}\text{-}(0.22) \times V\text{-}(1.03)$, where the excretion of calcium, oxalate (Ox), magnesium and citrate (Cit) was expressed in millimoles excreted during the period and urine volume (V) in litres. A Tiselius index > 2.0 carries a high risk of calcium oxalate crystallisation [14]. Participants were instructed to maintain a balanced diet throughout the study and to refrain from taking excessive amounts of vitamin C.

Collected data were tabulated using Microsoft Excel (Microsoft Office 2013) to facilitate interpretation. Results were imported to IBM SPSS Statistics 23 (IBM Corp, Armonk, NY). A Mann–Whitney U test was used to compare the differences in baseline demographics between Group 1 and Group 2. A Wilcoxon signed-rank test was used to compare the results obtained after cranberry supplementation to those obtained at trial entry. Results are reported as median [interquartile range (IQR)]. A p value of < 0.05 was considered statistically significant. The study was approved by the local research and ethics committee.

Results

Fifteen participants completed the study (nine male, six female). One participant was excluded due to a grossly abnormal baseline urine collection. Two participants voluntarily withdrew from the study prior to completion. Median age did not differ between groups [28 (24–32) vs 27 (26–30), $p = 0.86$]. There was a similar gender balance between both groups [group 1 = 67% male (4/6), group 2 = 56% male (5/9), $p = 0.66$]. Tables 1 and 2 show median values of urinary calcium, oxalate, sodium, potassium, urea, creatinine, uric acid, magnesium and citrate, in addition to the calcium oxalate crystallisation (Tiselius) index, before and after cranberry supplementation. Mean percentage change in excretion variables is also shown.

Table 1 Results of urinalysis prior to and 14 days after supplementation with cranberry tablets

	Median [IQR] (pre)	Median [IQR] (post)	Median % change	p value
Calcium	6.50 (3.90–16.0)	6.25 (1.25–12.76)	− 31.1	0.17
Oxalate	0.42 (0.17–1.12)	0.91 (0.36–1.30)	52	0.24
Sodium	214.72 (139.38–410.77)	274.60 (115.56–331.30)	− 16	0.75
Potassium	125.68 (91.42–258.50)	143.05 (126.35–163.62)	22	0.91
Creatinine	27.72 (19.83–50.87)	28.76 (21.20–35.27)	0.6	0.60
Uric acid	5.83 (4.81–9.41)	9.84 (6.98–14.00)	48	0.03*
Magnesium	10.46 (7.16–17.24)	10.40 (8.25–12.26)	10	0.91
Citrate	3.60 (1.80–4.04)	3.09 (1.63–3.64)	− 11	0.25
Volume (L)	1.91 (1.29–2.64)	1.87 (1.25–2.44)	− 1.6	0.75
Tiselius index	1.22 (0.63–3.96)	3.93 (0.98–9.58)	25	0.04*

All electrolytes values in mmol/24 h

*Represents p-value < 0.05

Table 2 Results of urinalysis prior to and 14 days after supplementation with cranberry tablets containing vitamin C

	Median [IQR] (pre)	Median [IQR] (post)	Median % change	*p* value
Calcium	8.19 (3.67–23.57)	13.92 (4.78–26.63)	21.7	0.09
Oxalate	0.49 (0.21–1.84)	1.30 (0.78–3.52)	106	0.02*
Sodium	200.56 (113.95–465.47)	198.91 (72.27–794.62)	50.5	0.31
Potassium	122.15 (84.44–31.66)	221.61 (91.33–640.41)	50.3	0.06
Creatinine	23.52 (5.39–86.50)	51.56 (13.70–93.68)	11.5	0.07
Uric acid	5.43 (3.41–20.76)	12.49 (3.64–35.01)	65.4	0.06
Magnesium	8.68 (5.38–28.68)	26.73 (5.66–42.17)	44.9	0.06
Citrate	2.74 (1.55–3.10)	2.54 (1.54–3.33)	− 13.5	0.86
Volume (L)	1.70 (1.16–3.90)	2.67 (1.64–4.69)	19	0.04*
Tiselius index	1.78 (0.89–6.06)	6.96 (1.66–16.34)	187.2	0.02*

All electrolytes values in mmol/24 h

*Represents *p*-value < 0.05

There was a statistically significant increase in the urinary oxalate excretion of participants taking cranberry tablets containing vitamin C compared to baseline measurements ($p=0.02$). Although urinary oxalate excretion also appeared to increase in participants taking cranberry tablets without vitamin C, this did not achieve statistical significance ($p=0.24$). Five of six participants taking cranberry tablets without vitamin C (83%) and seven of nine participants taking cranberry tablets with vitamin C (77%) had increased oxalate excretion following supplementation. Individual changes in urinary oxalate from baseline are shown in Fig. 1.

There was a statistically significant increase in the Tiselius index of participants taking cranberry tablets without vitamin C ($p=0.02$) and also in those taking cranberry tablets containing vitamin C ($p=0.04$). Individual changes in Tiselius index from baseline are shown in Fig. 2. The median change in oxalate excretion was larger in participants taking cranberry tablets containing vitamin C compared to those taking cranberry tablets without vitamin C (1.15 vs 0.10 mmol/day, $p=0.113$). There was no significant difference in the mean change in Tiselius index between the two groups (4.54 vs 2.42 mmol/day, $p=0.61$).

Participants in both groups had a significant increase in uric acid excretion following supplementation (Tables 1, 2). The percentage increase in uric acid excretion appeared to be more pronounced in patients taking cranberry tablets containing vitamin C compared to those without (65.4 vs 48%, respectively); however, this difference was not statistically significant ($p=0.776$). Individual changes in uric acid excretion from baseline are shown in Fig. 3.

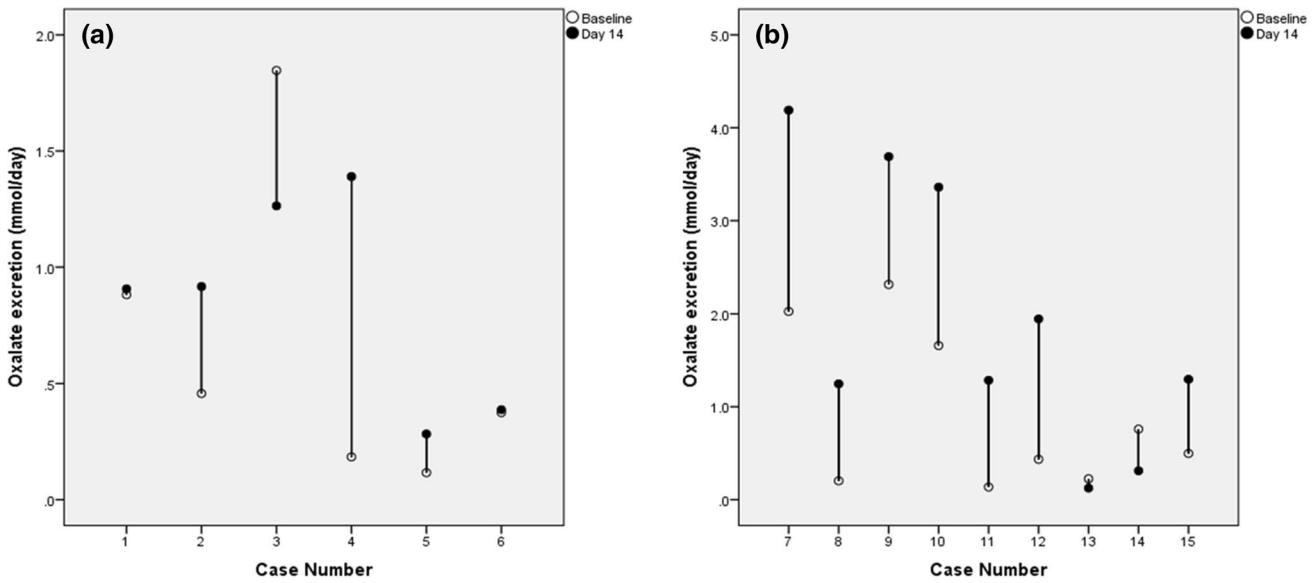

Fig. 1 Individual variation in oxalate excretion. **a** Cranberry-only tablets. **b** Cranberry tablets containing vitamin C

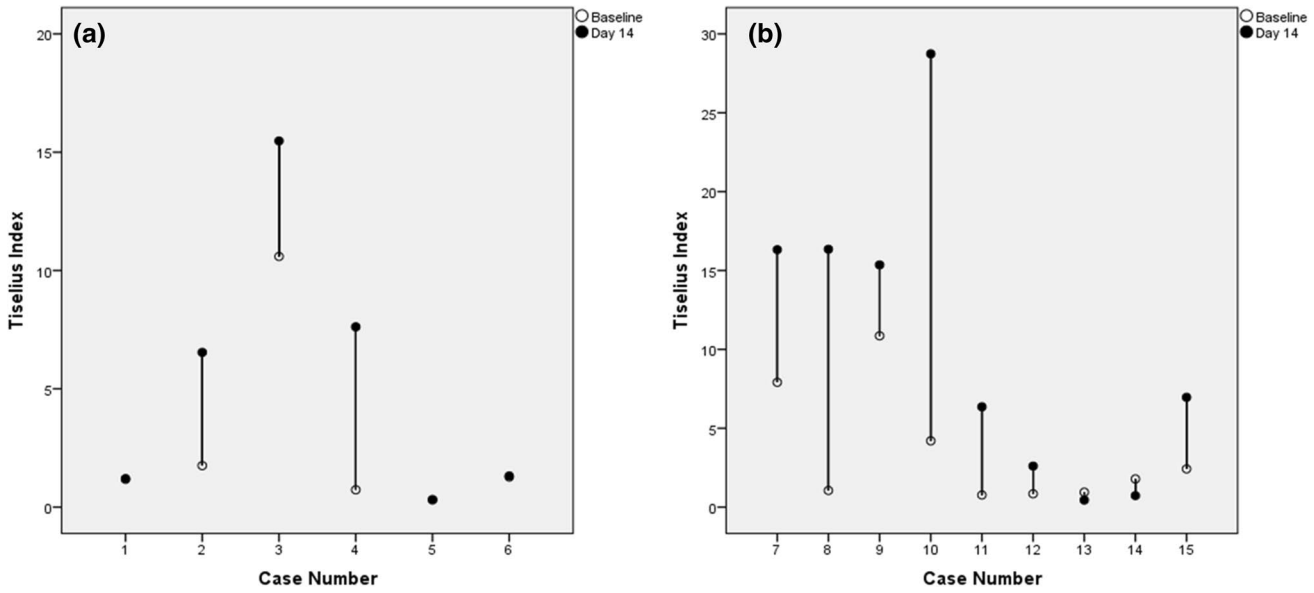

Fig. 2 Individual variation in Tiselius index. **a** Cranberry-only tablets. **b** Cranberry tablets containing vitamin C

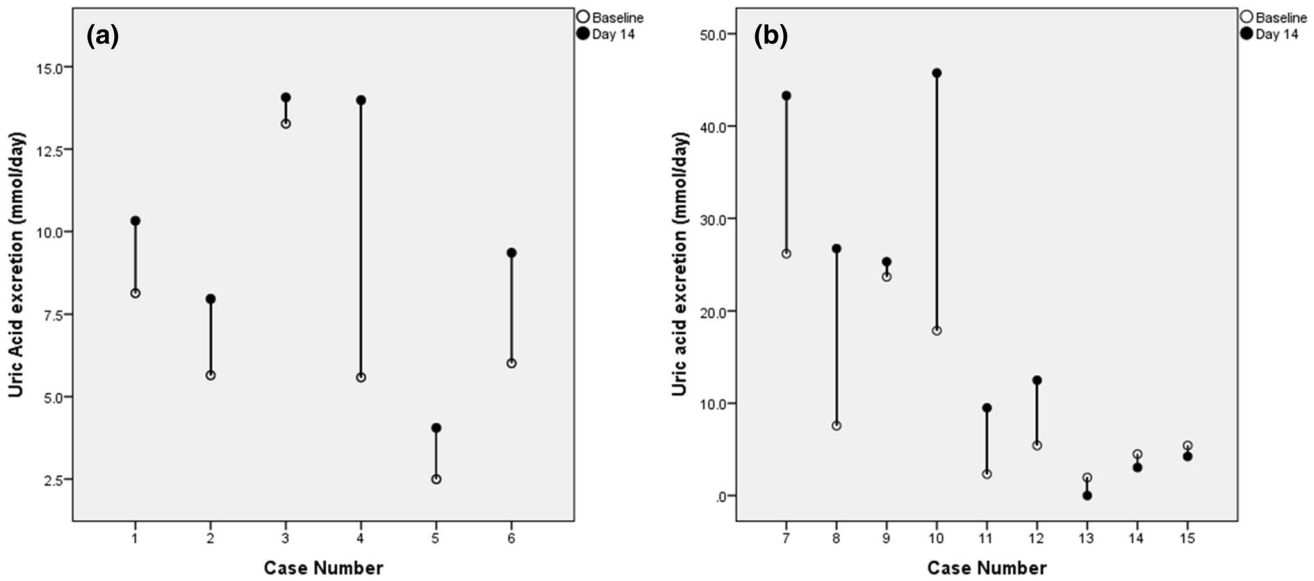

Fig. 3 Individual variation in uric acid excretion. **a** Cranberry-only tablets. **b** Cranberry tablets containing vitamin C

Discussion

The majority of renal stones are composed of calcium oxalate. A number of factors predispose to the formation of calcium oxalate stones including hypercalciuria, hyperoxaluria and hyperuricosuria [15]. Oxalate excretion is considered the most critical of these factors with studies showing that calcium oxalate crystallisation is more sensitive to incremental increases in oxalate excretion than similar increases in calcium excretion [16, 17]. Hyperoxaluria has been found in almost 20% of patients with recurrent nephrolithiasis [18].

Cranberries are often recommended to patients with recurrent urinary tract infections, due to their reported inhibition of bacterial adherence to the bladder urothelium. However, cranberries concentrates may contain high levels of oxalates, something which is frequently omitted from the listed ingredients on product labelling. In fact, previous studies have estimated that concentrated cranberry juice may contain as much as 84 mg of oxalate per litre [19]. The bioavailability of oxalates in cranberry tablets is unknown.

This study found that participants taking cranberry tablets containing vitamin C had a significant increase in mean oxalate excretion and Tiselius index. Participants taking cranberry tablets without vitamin C also had an increase in mean oxalate excretion and Tiselius index; however, this finding was not statistically significant. Three participants had a decrease in oxalate excretion following supplementation. It is not clear why this occurred and due to the small sample size it was not possible to adjust for potential confounding factors, e.g. age, gender and weight. These results are similar to a smaller study by Terris et al. which examined the effect of cranberry supplementation on five healthy volunteers [20]. It is not clear whether the cranberry tablets used in the study were fortified with vitamin C; however, all participants experienced an increase in daily oxalate excretion. The mean increase was 43.4%. Three further studies examining the effect of cranberry juice on oxalate excretion did not find any change in urinary oxalate excretion following supplementation [19, 21]. The potential reasons for this discrepancy are unclear; however, there may be an undocumented difference in the bioavailability of oxalate and/or vitamin C between both forms of supplementation. It has been shown previously that anthocyanidins are lost in juice processing; therefore, it is possible that some of the other nutrient contents of cranberries are also altered during the manufacturing process [22].

Cranberries are a natural source of vitamin C. They were taken by sailors to prevent scurvy and contain an estimated 18% of the recommended daily allowance of vitamin C [23]. Surprisingly, further to the naturally occurring vitamin C content of the berries, almost all commercially available cranberry tablet preparations are also fortified with additional vitamin C. This gives cranberry tablets, in particular, an exceptionally high vitamin C content when compared to other cranberry products. Vitamin C can be metabolised to oxalate and has been shown by a number of studies to increase urinary oxalate excretion when taken in high doses [8–12]. Therefore, it is not surprising that participants in our study who were taking cranberry tablets which had been fortified with vitamin C were found to have larger increases in oxalate excretion.

Our study also found a significant increase in uric acid excretion following cranberry supplementation. This was a new finding. One previous study found a non-significant increase in daily uric acid excretion and a significant increase in relative supersaturation of uric acid following ingestion of cranberry juice [24]. Two previous studies showed no change in uric acid excretion following ingestion of cranberry tablets [20] or juice [19]. Another study found a slight decrease in daily uric acid excretion but an increase in the overall concentration of dissociated uric acid following supplementation with cranberry juice [21]. Most fruits (including berries) are low in purine; therefore, it is unclear why there was an increase in uric acid excretion found in our study.

The present study shows that supplementation with cranberry tablets can alter urinary oxalate and uric acid excretion, particularly in supplements which are fortified with vitamin C. Both of these parameters are proven risk factors in the formation of renal calculi. Patients with a history of nephrolithiasis should be counselled regarding the use of products containing cranberry, particularly those fortified with vitamin C. Manufacturers of cranberry supplements should label their products to caution patients regarding their use in those at risk of renal stone formation.

Authors contribution REJ: data collection, data analysis, manuscript writing/editing. MCF: data collection, manuscript writing/editing. LJ: data collection. FK: data collection. AS: data analysis. CV: data analysis. LTH: manuscript writing/editing. MRP: protocol/project development, manuscript writing/editing.

Compliance with ethical standards

Conflict of interest None.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Hutchens AR (1992) A handbook of Native American herbs. Shambhala Publications
2. Kinney AB, Blout M (1979) Effect of cranberry juice on urinary pH. Nurs Res 28:287–290
3. Howell AB, Vorsa N, Marderosian AD, Foo LY (1998) Inhibition of the adherence of P-fimbriated *E. coli* to uroepithelial surfaces by proanthocyanidin extracts from cranberries. N Engl J Med 339:1085–1086
4. Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA (1994) Reduction of bacteria and pyuria after ingestion of cranberry juice. JAMA 271:751–754
5. Luís Â, Domingues F, Pereira L (2017) 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 198(3):614–621
6. https://nccih.nih.gov/health/cranberry
7. Baxmann AC, De OG, Mendonca C, Heilberg IP (2003) Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Kidney Int 63(3):1066–1071
8. Levine M, Conry-Cantilena C, Wang Y et al (1996) Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 93:3704–3709

9. Tiselius HG, Almgard LE (1977) The diurnal urinary excretion of oxalate and the effect of pyridoxine and ascorbate on oxalate excretion. Eur Urol 3:41–46
10. Chalmers A, Cowley D, Brown J (1986) A possible etiological role for ascorbate in calculi formation. Clin Chem 32:333–336
11. Urivetzky M, Kessaris D, Smith AD (1992) Ascorbic acid overdosing: a risk factor for calcium oxalate nephrolithiasis. J Urol 149:1215–1218
12. Pearle MS (2003) Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Int Braz J Urol 29(2):167
13. Feres MC, Bini R, De Martino MC, Biagini SP, de Sousa AL, Campana PG, Tufik S (2011) Implications for the use of acid preservatives in 24-hour urine for measurements of high demand biochemical analytes in clinical laboratories. Clin Chim Acta 412(23–24):2322–2325
14. Tiselius HG (1991) Aspects on estimation of the risk of calcium oxalate crystallization in urine. Urol Int 47(4):255–259
15. Ramello A, Vitale C, Marangella M (2001) Epidemiology of nephrolithiasis. J Nephrol 13:S45–S50
16. Lewandowski S, Rodgers AL (2004) Idiopathic calcium oxalate urolithiasis: risk factors and conservative treatment. Clin Chim Acta 345:17–34
17. Rodgers A (1999) Aspects of calcium oxalate crystallization: theory, in vitro studies, and in vivo implementation. J Am Soc Nephrol 14:351–354
18. Laminski NA, Meyers AM, Kruger M, Sonnekus MI, Margolius LP (1991) Hyperoxaluria in patients with recurrent calcium oxalate calculi: dietary and other risk factors. Br J Urol 68(5):454–458
19. McHarg T, Rodgers A, Charlton K (2003) Influence of cranberry juice on the urinary risk factors for calcium oxalate kidney stone formation. BJU Int 92(7):765–768
20. Terris MK, Issa MM, Tacker JR (2001) Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis. Urology. 57(1):26–29
21. Gettman MT, Ogan K, Brinkley LJ, Adams-Huet B, Pak CY, Pearle MS (2005) Effect of cranberry juice consumption on urinary stone risk factors. J Urol 174(2):590–594
22. White BL, Howard LR, Prior RL (2011) Impact of different stages of juice processing on the anthocyanin, flavonol, and procyanidin contents of cranberries. J Agric Food Chem 59(9):4692–4698
23. The Food Processor, Version 10.12.0, ESHA Research, Salem, Oregon, USA
24. Kessler T, Jansen B, Hesse A (2002) Effect of blackcurrant-, cranberry-and plum juice consumption on risk factors associated with kidney stone formation. Eur J Clin Nutr 56(10):1020