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Literature Review

Cranberry in radiotherapy: dispelling the myths. A review of the literature

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Abstract

Background: Therapeutic radiographers routinely offer advice to patients regarding treatment-related side effects. Cranberry has long been used as a natural remedy for several health complaints and has more recently been suggested as having a role in the treatment and prophylaxis of urinary tract infection (UTI) and symptoms.

Purpose: The aim of this review was to investigate whether there is a place for cranberry as part of the management of radiation cystitis caused by radiotherapy treatment of pelvic cancers, in order to aid therapeutic radiographers in tailoring their advice regarding pelvic side effects.

Materials and methods: A structured search was carried out using PubMed, CINAHL, Scopus and Cochrane Library databases. A total of 25 articles were selected for review.

Results: Themes of mechanism of action of cranberry, composition of cranberry products, cranberry and UTI, use of cranberry in radiotherapy and further issues to consider were identified and explored.

Conclusion: A lack of high-quality data was identified in the literature reviewed and no firm evidence was found to support the continued recommendation of cranberry as part of management of radiation induced urinary tract side effects. Well-designed randomised controlled trials are required before further recommendations regarding the use of cranberry in radiotherapy are made.

Keywords: Cranberry; radiation cystitis; radiotherapy; urinary tract infection

INTRODUCTION

Part of a therapeutic radiographer's day-to-day role is to give patients advice and information on ways of minimising the side effects of radiotherapy that might otherwise be dose limiting, or create issues of non-compliance with prescribed treatment courses. For many patients undergoing radiotherapy to the pelvis, radiation-induced cystitis and other urinary symptoms can be uncomfortable, painful side effects. A study by Peeters et al.[1] reported acute

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genitourinary (GU) side effects [according to the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria scale] of grade 2 in 41% and grade 3 in 13% of patients undergoing conformal radiotherapy to the prostate gland. Additionally, Majewski and Tarnawski[2] reported acute bladder toxicity rates of ≥3 in 5% of patients, however, their retrospective study covered a timeframe from 1975 to 1995 when dose escalation was less common, conformal techniques were less sophisticated and also included radiotherapy delivery by cobalt-60 teletherapy units. These approaches offer some insight into the generally lower toxicity rates, however, they also reported seven patients who failed to complete the prescribed course due to toxicity, although it was not specified whether this was due to GU or gastrointestinal (GI) effects. Regardless, these studies highlight that a number of patients can suffer significant bladder and urinary system toxicity related to radiotherapy, which, for the individual patient, can be distressing and can require intervention.

Historically, Native Americans used cranberry for food and in poultices and use of cranberry in North America is still considerable.[3] In the popular press, particularly publications aimed at women, cranberry juice has been promoted as a 'folk remedy', 'natural remedy' or 'complementary or alternative' medicine (CAM), which may aid in reducing the symptoms of cystitis. A recent paper surveying nurses' use of CAM indicated that 19% ($n = 103$) of nurses responding used cranberry juice for urinary tract infection (UTI).[4] These factors may help to explain the increasing anecdotal evidence suggesting that some therapeutic radiographers are routinely recommending that patients undergoing pelvic radiotherapy might drink cranberry juice/cranberry cocktail to help alleviate symptoms associated with radiation cystitis.

The purpose of this review of literature is twofold. First, it will present evidence and discussion on the use of cranberry juice (and other cranberry products) with respect to UTI and urinary symptoms/side effects. Second, it will relate this to the advice regarding use of cranberry, which may be given by therapeutic radiographers to patients undergoing pelvic radiotherapy.

SEARCH STRATEGY

The literature search was undertaken electronically using the PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus and Cochrane Library databases with a further search undertaken using Google Scholar. Search terms used were various combinations of Cranberry, Vaccinium Macrocarpon, cystitis, radiation, radiotherapy, urin*. Initial search results yielded ~700 articles. Articles were excluded if they referred to in vitro rather than in vivo studies and published in a language other than English. On initial review of articles, it was noted that the first article proposing the currently accepted mechanism of action of cranberry in UTI was published in 1994 by Avorn et al.,[5] therefore a further limit excluding articles published before 1994 was employed. Articles referring to paediatric populations were excluded in order to return literature related to older populations and therefore most representative of the age demographic of patients who attend for pelvic radiotherapy. The reference lists of the final selection of articles were also scanned and a further few articles identified, producing a total of 45 articles potentially suitable for attention. Of these, 25 articles were deemed suitable for appraisal and these produced the five themes under which this review is structured.

Mechanism of action of cranberry

The mechanism of action of cranberry has been debated and investigated for several decades. Avorn et al.[3,5] and Raz et al.[6] report studies from the 1920s to 1970s where acidification of urine (due to benzoic acid in cranberries being excreted as hippuric acid) was suggested to increase bacteriostatic conditions. However, the Avorn et al. study[5] concluded that the amount of cranberry consumed would not increase the levels of hippuric acid enough to lower urinary pH to the levels required to create a bacteriostatic environment within the bladder. Subsequent studies cite the most likely mechanism of action as being due to metabolites of the proanthocyanadins (PAC) found in cranberry preventing P-fimbriated *Escherichia coli* (E. Coli) and other organisms from adhering to the

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epithelia and mucosa of the urinary tract, with these non-adherent organisms being washed out of the bladder during micturition.[3,5,7–13] In one study, E. Coli was found to be the aetiological agent in around 80% of episodes of UTI.[14] PAC are a type of tannin that, in the cranberry plant, appear to act as part of the plant's defence system against microbes.[3,15] PAC have antioxidant properties, one of which being enzyme inhibition[16] and it is this property that appears to potentiate the anti-adherence of bacteria reported by the previously mentioned studies.

Composition of cranberry products

There are a number of confounding issues when comparing the results from studies applying cranberry to treat/prevent UTI and urinary symptoms. The first is being able to quantify the levels of PAC contained in a particular product and the second is provision of a product that is tolerable and palatable for the participants.

Most commercially produced cranberry juice cocktails such as that produced by Ocean Spray™ Cranberries Inc. typically contain ~25% cranberry juice mixed with other ingredients such as apple juice, water, sweeteners (either fructose or artificial sweeteners depending on whether it is marketed as 'low calorie') and vitamin C. This type of drink was used in studies carried out by Avorn et al., Barbosa-Cesnik et al., Campbell et al., Cowan et al. and McMurdo et al.[5,17–20] Other papers reported use of cranberry juice concentrate diluted in carrying quantities of water[21,22] or diluted cranberry–lingonberry juice concentrate.[14] Three studies[23–25] involved the use of tablets or capsules containing concentrated cranberry extract. One[26] used enteric-coated cranberry extract tablets and another[12] used sweetened, dried cranberries. The problem with attempting any comparison of these studies is the lack of standardisation related to the 'dose' of cranberry administered. This dose is variously reported as a volume of juice or cocktail, diluted cranberry concentrate, cranberry extract and dried cranberry, with few studies reporting the actual PAC content of the particular cranberry product. PAC content has been reported as 100 mg/day from 400 mg of concentrated cranberry extract,[23] 224 mg/day from 16 oz of 27% low-calorie cranberry juice cocktail,[19] 30% from 200 mg highly standardised and titrated cranberry extract[26] and 11·175 μg/g concentration from 300 mL cranberry juice drink.[27] There is no consistency across these studies regarding PAC dose and none compared different concentrations of PAC. Combined with the majority of studies that report only the cranberry dose and not PAC content, questions therefore must be posed regarding the reliability of these studies.

One issue with cranberry products is that of palatability. This is related to the flavour and acidity of cranberry products, hence most cocktails and products are sweetened and diluted with water or other juices to improve this. Compliance rates for ingestion of these sweetened juices/cocktails is good with very few studies reporting issues related to taste, however, Stothers[28] reported that a minority of patients complained of reflux and others taking the tablet form of cranberry extract had problems with the size of the tablet. Reports of tolerability of cranberry drinks are associated with two main issues: the sugar content of the juice or cocktail, with some studies choosing to use a low-calorie version sweetened with saccharine,[5,19] or the volume of juice consumed being that which could be safely integrated into the diet of diabetic patients.[18,26]

Cranberry and UTI

In undertaking this review, it was interesting to note that out of the final selection of 45 papers, nearly half (21) are reviews. This reflects the conflicting nature of the results of some of the studies reviewed and the difficulty in carrying out systematic reviews of good-quality randomised controlled trials (RCT) due to the wide range of methodologies, sample sizes, populations and doses of cranberry used. This is compounded by the very limited number of published RCT studies. Indeed, many of the reviews echo the sentiment that there is limited good-quality evidence from which to draw conclusions regarding the efficacy of cranberry products in either prophylaxis or treatment of UTI. The table summarises six RCT examined

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Table 1. Summary of RCT utilising cranberry in the treatment and/or prophylaxis of UTI

Study	*n*	Study design intervention	Results
Avorn et al.[5]	153 Elderly women	300 mL cjc or pj daily for 6 months	Bacteriuria with pyuria found in 28·1% of urine samples in placebo group versus 15·0% in cranberry group. Subjects in cranberry beverage group more likely than placebo to transition from bacteriuric-pyuric to non-bacteriuric-pyuric urine on successive months
Barbosa-Cesnik et al.[19]	319 College women aged 18–40 with current and past history of UTI	8 oz of 27% low-calorie cjc or pj 2× daily for 6 months	Overall UTI recurrence rate was 16·9: 19·3% in cranberry group versus 14·6% in placebo group; log-rank $p = 0{\cdot}21$). No significance found
Kontiokari et al.[14]	150 Women with UTI mean age 30 (range not reported)	50 mL of 7·5 g/1·7 g cranberry–lingonberry juice concentrate daily for 6 months versus 100 mL lactobacillus drink 5 × per week for 1 year versus no intervention	20% reduction in absolute risk of recurrence of UTI in cranberry group compared with control group. No difference seen for lactobacillus
McMurdo et al.[20]	376 ≥60 years old inpatients	150 mL cranberry juice or 150 mL placebo beverage 2× daily for 35 days or until hospital discharge	21/376 (5·6%) had at least one symptomatic UTI (14 in placebo group and 7 in cranberry juice group); RR 0·51 (95% CI 0·21–1·22, $p = 0{\cdot}122$). No significance found
McMurdo et al.[27]	137 Women aged ≥45 with history of UTI	Capsules of 500 mg of cranberry extract or 100 mg of trimethoprim for 6 months	39/137 (28%) had symptomatic antibiotic-treated UTI (25 in the cranberry group and 14 in the trimethoprim group); the difference in proportions was RR 1·616 (95% CI: 0·93, 2·79) $p¼$ 0·084
Stothers[28]	150 sexually active women with history of UTI, 21–72-year old	pj + placebo tablets (pt) versus pj + 1:30 concentrated ct, versus pure cj + pt. Tablets were taken twice daily, juice 250 mL 3× daily	Participants experiencing at least 1 UTI during treatments was 16 (32%) in placebo group, 10 (20%, $p < 0{\cdot}05$) in the juice group and 9 (18%, $p < 0{\cdot}05$) in the tablet group. The mean no. of UTI during year following treatment was 0·72 in placebo group, 0·30 in the juice group ($p < 0{\cdot}05$) and 0·39 in tablet group ($p < 0{\cdot}05$)

Abbreviations: CI, confidence interval; cjc, cranberry juice cocktail; ct, cranberry tablets; pj, placebo juice; RCT, randomised controlled trial; RR, relative risk; UTI, urinary tract infection.

by the authors of those 21 review papers. Not all RCTs mentioned in the studies are included – excluded are those relating to paediatric cases and those related to bladder problems in spinal injuries patients (indwelling catheterisation is commonplace for patients with spinal injuries, therefore increasing the prevalence of UTI in this population and therefore findings of these studies would not compare with general populations). However, the brief details given in the table highlight the previously mentioned difficulties in evaluating the literature in this topic area. Essentially, what these studies and the reviews that examined them have indicated is that there is little or no consistent, significant or detailed data to provide evidence for the use of cranberry in the treatment of UTI and its symptoms. Rather, this limited evidence points towards some prophylactic effect in younger women with previous history of UTI and some activity in older women, but none of the results were statistically significant (Table 1).

Use of cranberry in radiotherapy

Only three studies to date have examined the use of cranberry in the radiotherapy setting. Because of their particular relevance to this review, they are summarised here. In 2003 Campbell et al.[18] carried out an RCT comparing the use of cranberry juice cocktail with apple juice in patients undergoing conformal

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external beam radiotherapy (EBRT) for prostate cancer. A total of 112 patients were randomised to receive either 354 mL 27% cranberry juice cocktail or 354 mL 100% apple juice per day in pre-packaged cartons, provided to the study free of charge by Ocean Spray Cranberries Inc. Juice was consumed for the duration of EBRT and 2 weeks following. Overall duration of radiotherapy is not reported in the study, but the reported total prescribed dose range of 64–70 Gy would indicate a 6–7-week course if a standard 2 Gy per fraction prescription is assumed. Patients were evaluated throughout their course of treatment using the International Prostate Symptom Score (IPSS) questionnaire. The study found no significant difference in levels of urinary symptoms between the two groups.

An RCT by Cowan et al.[17] examined the effectiveness of cranberry in patients undergoing pelvic radiotherapy for either bladder or cervical cancers in reducing UTI and urinary side effects. In this study, 128 participants were randomised to receive either cranberry juice or placebo beverage for the duration of their treatment – no details of dosage are given, however, results taken indicate that across the duration of treatment patients had consumed volumes of juice totalling ≥16,000 mL. Again, the juice and placebo were provided by Ocean Spray Cranberries Inc. so it can be assumed that the juices had a similar composition to those used in the Campbell study (27%). As with the Campbell et al.[18] study, no significant differences in rates of UTI or levels of side effects were seen between the two groups, however, the team acknowledged that their study was underpowered due to issues in recruitment resulting in only half the expected number of participants.

It is worth reiterating at this point that cranberry juice drinks typically contain ~25% juice. Current products manufactured by Ocean Spray™ see the cranberry juice mixed with either water and sugar (cranberry classic) or grape juice (100% juice, cranberry blend) with 25% cranberry juice present in each (source: www.oceanspray.co.uk).

The most recent study, published in 2012 by Bonetta and Di Pierro[26] is a non-randomised, placebo-controlled trial examining the effect of cranberry extract on UTI and urinary symptoms related to EBRT for prostate cancer. A total of 370 patients receiving intensity-modulated radiotherapy for prostate cancer were consecutively recruited to receive either 200 mg cranberry extract or placebo per day in the form of enteric-coated tablets. The cranberry extract was specifically formulated to contain 30% PAC. This use of cranberry extract in tablet form was in recognition of design limitations associated with the use of manufactured juice drinks in the previous two studies[17,18] and that in those studies, PAC content was not specified. Patients were regularly screened for lower urinary tract infection (LUTI) and self-reported levels of bladder symptoms. The bladder symptoms were assessed against the Boyarsky scale (0 = no symptoms, 1 = burning sensation during urination, 2 = frequent burning or pain during urination more than 50% of times, 3 = continuous burning sensation or pain during urination).[26] The authors report a statistically significant lower rate of UTI in the group receiving cranberry extract, with an associated reduction in radiotherapy side effects in the same group. Upon inspection these data appear promising; however, there are several problems inherent in the study design. The major problem is the non-randomisation of participants. No information is given as to how participants' groups were stratified; therefore, the authors' statement of statistical significance is erroneous due to systematic bias. Additionally, no information in the results section is given to explain how the purported significance was achieved. In their examination of reported side effects, the authors have cited several statistical testing methods; however, it is not clear whether these tests were the most appropriate for their data and thus the reported results are confused and lacking validity.

In examining all three studies, an obvious factor relating to study design is lack of a 'pure' control group. Participants in the second group of each study received a placebo and therefore without the third pure control group, it is impossible to measure the placebo effect. This effect has been acknowledged widely as a confounding factor in this type of study if not

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accounted for,[29] especially if results rely on subjective measures; Campbell et al.[18] discuss this issue as a limitation in their study.

Further issues to consider regarding use of cranberry in radiotherapy

In most of the studies reviewed where cranberry juice drinks were utilised, an inherent effect on the patient would be that by participating, they may be increasing their overall fluid intake. Indeed Stothers[28] reported that some results were likely to be due to this increased fluid intake and the resultant 'washout' effect. Without firm evidence to the contrary, this could be one mechanism behind reduced rates of UTI/symptoms also seen in other studies. Another issue for radiographers to consider when giving advice to patients is that of drug interactions. Evidence suggests that 'natural remedies' are not considered harmful by those who use them[30] and therefore advice regarding cranberry (which could be considered a natural remedy) may be given without the consideration of potential interactions such as that reported with Warfarin[31,32] – a drug many elderly patients may be taking, unbeknown to the staff treating them. These two papers highlight an interaction between cranberry and Warfarin whereby INR (International Normalized Ratio—ratio of prothrombin time to normal sample) of patients becomes raised, indicating a higher risk of bleeding. Bearing in mind that haematuria is common in patients undergoing pelvic radiotherapy, either as a tumour effect or surgical morbidity; this potential interaction should not be ignored.

CONCLUSION

The purpose of this review was to consider the evidence related to the effect of cranberry on UTI and bladder symptoms/side effects in order that therapeutic radiographers are able to justify and demonstrate clinical reasoning regarding the advice they give to patients undergoing pelvic radiotherapy. The mechanism of action of PAC on cystitis of pathogenic origin appears to be due to inhibition of adherence of pathogens to the bladder wall. No firm evidence is currently available to recommend the specific dose of PAC required to give a statistically significant therapeutic effect in groups of patients with similar demographic to most of those encountered in radiotherapy departments. Studies focussing specifically on radiation-mediated bladder effects have produced inconclusive or misleading results, which do not provide evidence to suggest that cranberry is effective in alleviating bladder-related side effects in patients undergoing pelvic radiotherapy. In addition, other research indicates that caution is required when suggesting cranberry, unless the Warfarin status of a patient is known.

Therefore, based upon this review of literature, it is suggested that there is currently no evidence to indicate that therapeutic radiographers should advise patients to ingest cranberry juice or cranberry extract products to help alleviate the bladder-related side effects of radiotherapy.

Future research should take the form of one or more RCT considering the following points of design. One trial arm should have no intervention in order to more fully assess the effect of placebo juices/tablets. PAC concentration must be considered and compared in order to determine an optimum 'dose' of cranberry. It would be useful to determine whether merely increasing fluid intake has any effect on symptoms of radiation cystitis in order to compare with patients given cranberry juice drinks. There may be value in comparing male and female responses, especially given the potential differences in irradiated volumes/radiotherapy dose prescriptions dictated by gender-specific anatomy. There may also be merit in qualitative research looking into patients perceptions regarding the benefits of cranberry. These considerations in the design of one or more RCT should provide the reliability required to produce more robust data.

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Conflicts of Interest

None.

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