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Cranberry juice decreases disease activity in women with rheumatoid arthritis

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ABSTRACT

Objectives: Studies have shown that cranberry (*Vaccinium macrocarpon*) has antiinflammatory and antioxidant effects; however, to our knowledge, the effects of cranberry juice consumption have not been studied in patients with rheumatoid arthritis (RA). The aim of this study was to verify the effect of cranberry juice consumption on several inflammatory biomarkers and on the disease activity of patients with RA.
Methods: A prospective study was conducted with 41 women diagnosed with RA. The disease activity measured by Disease Activity Score 28 (DAS28) and anticyclic citrullinated peptide (anti-CCP) antibodies, and several inflammatory and biochemical biomarkers were analyzed. The control group ($n = 18$) maintained their usual diet. The cranberry group ($n = 23$) consumed 500 mL/d of low-calorie cranberry juice.
Results: Regarding the baseline values, the cranberry group presented a decrease in the values of DAS28 ($P = 0.048$) and anti-CCP ($P = 0.034$) after 90 d of treatment, whereas changes in inflammatory biomarkers were not found.
Conclusion: The present study indicated that cranberry juice decreases disease activity and therefore has beneficial effects for RA patients, although larger and long-term studies are needed to definitively probe this effect and to clarify the mechanisms involved.

Introduction

The term *rheumatoid arthritis* (RA) was used >150 y ago to distinguish it from other forms of arthritis, such as acute rheumatism and gout [1]. RA is characterized by the progressive destruction of the joints and by extraarticular involvement and is thus classified as a systemic inflammatory disease. The disorder likely develops in individuals who are genetically susceptible to abnormal immune responses and who have been exposed to specific environmental factors. RA affects millions of people worldwide—1% of the population, and an estimated 2 million people in the United States [2]. In the past 40 y, the prevalence of RA has not decreased, and life expectancy for patients with the diease is significantly lower than that of the heathy population [3,4], with women three times more likely to be affected than men [5].

Patients with RA have 33% to 50% of the causes of early mortality owing to cardiovascular diseases, including ischemic coronary disease and stroke [6]. It has been demonstrated that the autoimmune activation of leukocytes leads to the production of cytokines and mediators of inflammation, oxidative stress, and endothelial dysfunction, which lead, in a coordinated way, to the development of atherosclerosis [7]. With the evolution of clinical research, an association between the ingestion of antioxidant nutrients and the decrease in the formation of free radicals has

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been demonstrated, and in other aspects related to the pathogenesis of RA [8], suggesting that these antioxidants effectively suppress the release of inflammatory cytokines, thereby decreasing reactive oxygen species [9] and have a protective effect against the development of RA [10].

Berries are important sources of micronutrients and bioactive components that are known to have cardiovascular health benefits [11]. The antioxidant properties of these fruits have been well documented in human studies and the cardiovascular effects observed are not only restricted to their antioxidant capacity [12]. Some studies have pointed to the benefits of cranberry on serum lipid profiles, blood pressure, endothelial function, and a variety of biomarkers of inflammation and oxidative stress [13]. Differently from the antioxidant effects, the antiinflammatory actions of cranberry are still controversial in the literature [14]. Although some authors verified a decrease in inflammation biomakers, such as C-reactive protein (CRP) [15,16], in healthy population with cranberry juice, our group reported that low-calorie cranberry juice had no effect on CRP levels and proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 in patients with metabolic syndrome (MetS) [17].

Therefore, considering that we are not aware of any report with cranberry in patients with RA and the possible benefits of cranberry juice ingestion in these patients, this study aims to evaluate the effects of cranberry juice consumption on the inflammatory biomarkers and disease activity of patients with RA.

Materials and methods

Patients

This study included 41 women with RA. The intervention and the control group had 23 and 18 participants, respectively. Patients with RA were selected from among the ambulatory unit of Rheumatology of the University Hospital of Londrina, Paraná, Brazil. None of the participants in the study presented heart, thyroid, renal, hepatic, gastrointestinal, oncologic, or other autoimmune diseases, and none were receiving estrogen replacement therapy or antioxidant supplements. Also, patients with renal impairment, B_{12} insufficiency, hypothyroidism, or hemolysis or those using drugs such as phenytoin, isoniazid and levodopa were excluded from the study to avoid interference with homocysteine results [18]. All of the individuals were non-smokers and did not drink alcohol on a regular basis. Patients who were taking antihypertensive drugs were not excluded and were allowed to continue taking the same dose of the drugs. None of the women followed a specific diet before the study began. The patients were instructed by a dietitian to maintain their usual diets, alcohol intake, level of physical activity, or other lifestyle factors throughout the intervention period. Non-compliance was verified in three patients from the intervention group.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving humans were approved by the Ethical Committee of the University of Londrina, Paraná, Brazil. Written informed consent was obtained from all patients.

Study design

Patients with RA were randomly assigned to one of two groups after stratification by age and waist circumference (WC): the control group ($n = 18$) was only directed to maintain their usual diet, whereas the intervention group ($n = 23$) ingested 500 mL/d of reduced-calorie cranberry juice. The women were told to avoid resting after meals to prevent unpleasant side effects. Both groups were evaluated at the beginning of the study and after 90 d. Interviews were performed to assure no change in lifestyle factors had occurred throughout the study. The nutrient composition of 500 mL of cranberry juice was as follows: 50 kcal, 0 g protein, 12.5 g carbohydrate, 0 g lipids, 0 g fiber, 75 mg f sodium, 150 mg vitamin C, 131.92 mg proanthocyanidins, 258.75 mg total phenolics, and 0.30 mg folic acid. Evaluation of clinical and laboratorial parameters was assessed at the beginning of the study and after 90 d.

Steps taken to optimize compliance

Several measures were taken to optimize and assess patient compliance. Boxes of cranberry juice were handed out at the initial interview and at the two later visits. The women were asked to bring back any unconsumed juice to assess unmonitored compliance. In addition, telephone interviews were performed to evaluate whether the patients were correctly using the supplement and the patients were asked to avoid lifestyle changes. Treatment adherence of the participants of the study was ~95%.

Clinical evaluation

Information on each patient's medical history was obtained by clinical evaluation performed by a rheumatologist. Information on the the use of medications, including nonsteroidal antiinflammatory drugs, corticosteroids, antimalarials, and antihypertensive drugs were recorded for each patient.

Anthropometric measurements and laboratorial parameters were assessed. Body weight was measured to the nearest 0.1 kg in the morning using an electronic scale, with individuals wearing light clothing and no shoes; height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. With the women standing, WC was measured midway between the lowest rib and the iliac crest. Patients were selected according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [19], and disease activity status was determined using the Disease Activity Status 28 (DAS28) by a blinded rheumatologist. The DAS28 considers 28 tender and swollen joint counts, general health (GH; patient assessment of disease activity using a 100-mm visual analog scale where 0 = *best*, 100 = *worst*), plus levels of erythrocyte sedimentation rate (ESR; mg/L). DAS28 values categorize patients into four different groups, namely, remission group: DAS28 $\leq$2.6; low disease activity group: DAS28 $<$2.6 to $\leq$3.2; moderate disease activity group: DAS28 $<$3.2 to $\leq$5.1; and high disease activity group: DAS28 $>$5.1 [19].

Biochemical and immunologic biomarkers

After fasting for 12 h, venous blood was drawn with ethylenediaminetetraacetic acid–coated sterile tubes (BD Vacutainer UltraTouch, Franklin Lakes, NJ, USA). Whole blood was allowed to stand for 30 min and then was centrifuged at 1500 *g* for 10 min. Plasma and serum samples were separated, divided into aliquots, and stored at −80°C for subsequent analysis.

Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein, triacylglycerol, and glucose levels were evaluated by a biochemical autoanalyzer (Dimension Dade AR, Dade Behring, Deerfield, IL, USA) using Dade Behring kits. Insulin analysis was performed by microparticle enzyme-linked immunoassay using Abbott AxSYM equipment (Abbott Laboratories). Homeostatic model assessment is an estimate of insulin resistance [20] and was calculated using the following formula:

Homeostatic model assessment–insulin resistance = fasting glucose (mmol/L) × fasting insulinemia (mU/L) / 22.5.

White blood cell, platelet, and ESR counts were determined using hematologic autoanalyzers. Serum CRP levels and rheumatoid factor (RF) titers were measured using a turbidimetric assay (C8000, Abbott, Architect Abbott Laboratories, Abbott Park, IL, USA). Serum ferritin levels, anticyclic citrullinated peptide (anti-CCP) antibodies, and total plasma levels of homocysteine, were determined with chemiluminescent microparticle assays (Architect, Abbott Laboratory). The reference value for anti-CCP antibodies used in the present study was $<$5 U/mL.

Statistical analyses

Categorical data were analyzed by Fisher exact test or the χ^2 test, as appropriate. The Wilcoxon matched pairs test was performed to verify changes from baseline (intragroup changes). The Mann–Whitney test was performed to compare baseline values and differences between treatment groups (intergroup changes). Data were expressed as the median and interquartile ranges (median IQR). All statistical analyses were performed using the IM SPSS, Version 24 (IBM, Armonk, NY, USA). The tests were two-tailed and $\alpha = 0.05$ indicated statistically significant results. The sample size was estimated statistically for each group considering a statistical power of 80% and the bilateral significance level of $P < 0.05$. The sample size was calculated to detect statistical differences of at least 10% in the parameters evaluated. The G*Power 3.1.9.2 program for Windows (http://www.gpower.hhu.de/) was used to calculate the sample size, based on mean and standard deviation for some of the parameters previously evaluated in other studies [21,22].

Results

Non-compliance was verified in three patients from the intervention group and thus this group ended the study with 20 participants. The demographic and clinical characteristics of the patients are presented in Table 1. There was no difference between groups regarding age, WC, BMI, ethnicity, disease duration, the presence of hypertension and diabetes mellitus, smoking habits, extraarticular signs, and drug treatments. The majority of patients were being

Table 1
Demographic and clinical characteristics in the control group and cranberry juice group of patients with rheumatoid arthritis at the baseline

	Control (n = 18)	Cranberry (n = 20)	P-value
Age, y	50.5 (40–60)	55 (51–65)	NS
WC, cm	104 (91–110)	97 (81–103)	NS
BMI, kg/m^2	30 (22–32)	26 (23–30)	NS
Ethnicity, C/NC (%)	16 (88.9)/ 2(11.1)	17 (85)/3(15)	NS
Disease duration, y*	10.5 (2.8)	10.8 (0.3)	NS
Hypertension, yes/no	8/10	6/14	NS
Diabetes, yes/no	1/17	2/18	NS
Tobacco use, yes (%)	2 (11.1)	0 (0)	NS
Physical activity, yes (%)	5 (27.8)	5 (25)	
Extra articular, yes (%)	0 (0)	3 (15)	NS
Methotrexate (%)	10 (62.5)	14 (70)	NS
Prednisone (%)	14 (77.7)	16 (80)	NS
Hydroxychloroquine (%)	8 (50)	6 (30)	NS

NS, non-significant; WC, waist circumference; BMI, body mass index; C, caucasian; NC, non caucasian.
*Student's t test. Data are shown in mean (± standard deviation). The Kruskall–Wallis test. Data are shown in median [interquartile ranges].

treated with steroids and one or more disease-modifying antirheumatic drugs in stable doses for ≥4 mo: prednisone 5 mg/d, methotrexate 15 mg/wk, and hydroxychloroquine 400 mg/d.

The parameters related to metabolic components presented by patients at baseline and after 90 d are shown in Table 2. HDL levels were higher in the cranberry group than in the control group at the beginning of the study. An increase in the values for fasting glucose were observed (P = 0.04 in both groups. Intergroup changes were not found after 90 d.

Table 3 shows the parameters related to disease activity and inflammatory status in all participants at the beginning of the study and after 90 d. There were no differences in the baseline values between the groups. At the end of the 90-d treatment period, compared with baseline values, the cranberry juice intervention group showed a significant reduction in DAS28 (P = 0.048) and in anti-CCP levels (P = 0.034). Differently from the ESR, which maintained about the same stable values after 90 d in the intervention group, the parameters that decreased DAS28 were the number of painful and swollen joints and global health evaluation (data not shown). Intergroup changes were not found after 90 d.

Figures 1 and 2 illustrate DAS28-ESR of each patient at baseline and after 90 d in both groups. Individualized analysis showed that 10 patients decreased DAS28 after cranberry ingestion (patients 2, 5, 6, 8, 9, 12, 13, 14, 18, and 19). In contrast, 5 patients increased DAS28 (patients 1, 3, 4, 7, and 15) and 5 patients maintained their values (patients 10, 11, 16, 17, and 20). On the other hand, 10 control group patients maintained DAS28 (patients 2, 5, 7, 8, 10, 12, 14, 16, 17, and 18), whereas 5 increased (patients 1,4, 9, 11, and 13) and 3 reduced their values (patients 3, 6, and 15).

Discussion

The main findings of this study confirm the hypothesis that daily consumption of 500 mL of cranberry juice for 90 d promotes an improvement of disease activity in women with RA. This effect was demonstrated by the statistically significant decrease in anti-CCP antibodies levels and a statistically significant decrease in the disease activity score measured by DAS28. Of note, we found a broad interindividual response to cranberry in the results of DAS28. There are a number of factors that may influence this finding, including genetic polymorphisms of transporters or metabolizing enzymes, environmental influences, and likely the composition of the gut microbiome [23]. Future studies with this specific objective are warranted to analyze this important issue.

Unfortunately, we have no explanations for the statistically significant increase in glucose levels in the two groups. We found studies on cranberry ingestion in healthy and obese individuals and in patients with type 2 diabetes mellitus type and MetS, which showed decreased glucose levels. We also found other studies in which the levels were maintained [11,16]. We are not aware of any study that has showed increased glucose levels with cranberry ingestion. However, even with these statistically significant increases, the values were within the reference values for blood glucose. HDL levels had statistically significant increased values in the cranberry group than in the control group at the beginning of the study. In turn, although not significant, the cranberry group showed decreased BMI values compared with the control group at the beginning of the study. Perhaps BMI has exerted some influence on the results of HDL levels.

Table 2
Evaluation of the metabolic components of the control and cranberry groups presented at baseline (T0) and after 90 d (T90)

	Control (n = 18)			Cranberry (n = 20)			
	T0^A	T90	P-value	T0^B	T90	P- value	P- value^{AXB}
HDL	54.5 (48–59)	51 (48–64)	NS	64.5 (51.5–80)	63 (49–79.5)	NS	0.044
LDL	129 (94–149)	128 (97–140)	NS	109 (88–136)	115 (90–125.5)	NS	NS
Total cholesterol	204 (174–234)	200.5 (178–233)	NS	207 (183–219.5)	204.5 (183–224.5)	NS	NS
Triacylglycerols	101.5 (72–154)	100 (80–172)	NS	120 (87–135.5)	115 (80.5–150.5)	NS	NS
Glucose	84.5 (77–92)	93 (88–102)	0.04	89.5 (81–96.5)	94 (90–106)	0.04	NS
Insulin	8.80 (5.90–13.7)	8.3 (5.60–14.6)	NS	8.5 (7.4–12.25)	8 (5.7–12.6)	NS	NS
HOMA-IR	1.94 (1.26–2.6)	2.01 (1.4–3.06)	NS	2.02 (1.51–2.63)	2.11 (1.27–3.14)	NS	NS
Homocysteine	10.07 (7.75–15.01)	10.39 (7.85–13.75)	NS	10.13 (8.23–11.93)	10.42 (8.6–13.21)	NS	NS

HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance; LDL, low-density lipoprotein; NS, non-significant.
Data are shown in median [IQR]. The Wilcoxon test was performed to verify changes from baseline (intragroup changes). The Kruskall–Wallis test was performed to compare differences between the baseline values and across treatment groups (intergroup changes).
^{AxB}represents differences between baselines.

Table 3
Evaluation of the disease activity and inflammatory components of the control and cranberry groups presented at the beginning of the study (T0) and after 90 d (T90)

	Control (n = 18)			Cranberry (n = 20)			
	T0[A]	T90	P-value	T0[B]	T90	P-value	P-value[AXB]
DAS28	3.59 (3.19–5.23)	3.52 (2.90–4.57)	NS	3.48 (2.68–4.65)	2.99 (2.18–3.58)	0.048	NS
Anti-CCP	6 (1.5–34.3)	5.55 (0.8–20.8)	NS	1.55 (0.55–86.1)	0.9 (0.5–75.95)	0.034	NS
RF	19.7 (13.5–49.3)	32.25 (4.1–54.9)	NS	7.55 (4.2–44.95)	7 (3.65–59.4)	NS	NS
ESR	32.5 (12–40)	20 (15–42)	NS	18.5 (6–32.45)	22 (5–33)	NS	NS
CRP, mg/L	5.55 (1.50–9.10)	3.95 (1.90–10.50)	NS	3.10 (1.45–8.60)	2.85 (0.85–10.65)	NS	NS
Leukocytes	6.35 (5.40–7.50)	6.43 (5.70–8.46)	NS	6.74 (4.89–7.90)	6.44 (4.09–8.08)	NS	NS
Ferritin	84.28 (46.45–157.5)	82.71 (50.79–174.02)	NS	73.35 (61.09–118.54)	90.86 (56.67–135.5)	NS	NS

anti-CCP, anticyclic citrullinated peptide; CRP, C-reactive protein; DAS, disease activity index; ESR, erythrocyte sedimentation rate; NS, non-significant; RF, rheumatoid factor. Data are shown in median [interquartile ranges]. The Wilcoxon test was performed to verify changes from baseline (intragroup changes). The Kruskall–Wallis test was performed to compare differences between the baseline values and across treatment groups (intergroup changes).
[AxB]represents differences between baselines.

Some types of autoantibodies act as markers for RA diagnosis, such as RF and several anticitrullinated protein/peptide antibodies including anti-CCP. Previous studies have demonstrated that anti-CCP antibodies are the most clinically important antibodies directed against antigens of the filaggrin-citrulline system. This test is especially relevant for the subgroup of patients in the initial phase of RA with a negative test for RF because it has a sensitivity of 70% to 75% and a specificity of ~95% [24]. Therefore, anti-CCP is observed very early in the evolution of RA and can be used as an indicator of progression and prognosis of the disease [24].

We are not aware of any study that has verified the effect of cranberry ingestion in patients with RA. Therefore, the comparison of the present work with others is not possible. Also, it is difficult is to explain the decrease verified in disease activity, shown by DAS28 and anti-CCP, without concomitant reduction in inflammatory status. However, some explanations can be suggested:

- the small number of participants;
- no available information on the cytokine levels, which were not performed and could give a deeper analysis of the inflammatory status; and
- no available information on oxidative stress, which also contributes to RA pathophysiology and could even precede the inflammatory events [25].

ESR and CRP, although nonspecific, are tests frequently used to monitor disease activity. The DAS28 uses a more simplified joint count of 28 joints, determining a numerical value for RA using the ESR or CRP as an inflammatory marker, but the levels of this second marker require more studies because differences between ESR and CRP have been demonstrated by some patients with RA, with tendencies to higher values of ESR and lower values of CRP [26,27]. Some studies in healthy individuals have reported that cranberry juice consumers had lower CRP levels than non-consumers [15,16]. In contrast, other reports have not found any significant change in inflammatory markers with cranberry in patients with type 2 diabetes mellitus [28], coronary artery disease [29], or MetS [30]. In a study performed by our group with patients with MetS, low-calorie cranberry juice (700 mL/d) given for 2 mo was not able to decrease CRP or IL-6 values [17].

Several mechanisms by which cranberry and its components would exert biological activities have been proposed. There is

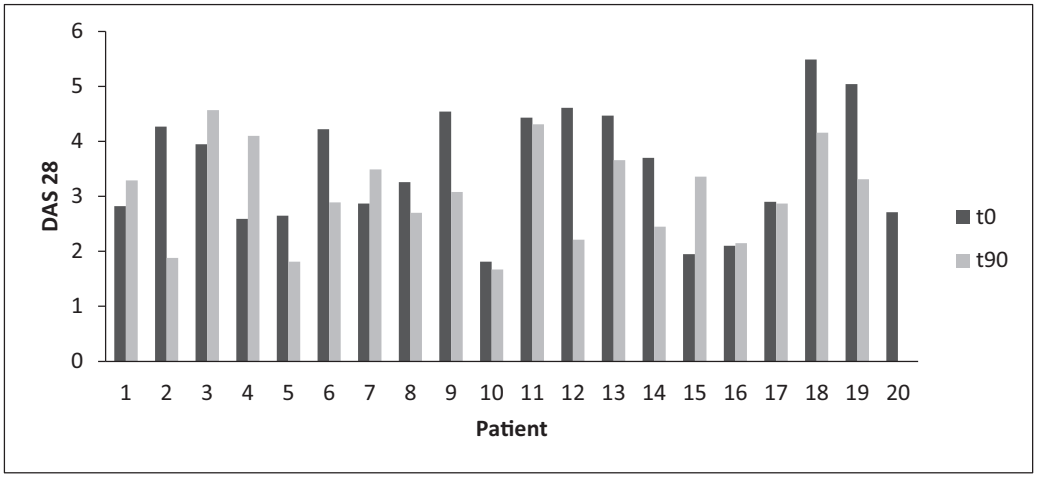

Fig. 1. DAS28 in the twenty patients who used cranberry at the beginning of the study (T0) and after 90 d (T90). DAS, disease activity status.

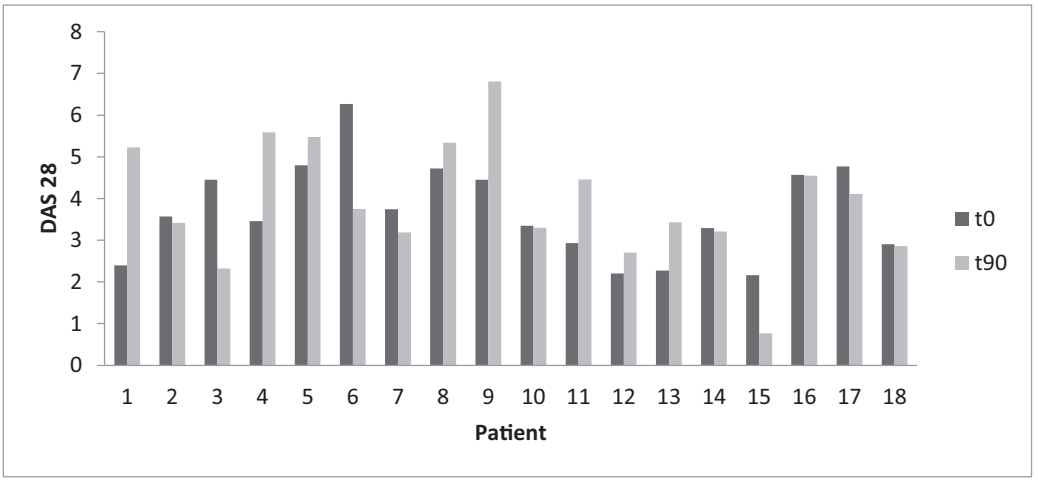

Fig. 2. DAS28 in 18 control group patients at the beginning of the study (T0) and after 90 d (T90). DAS, disease activity status.

evidence that quercetin, a flavonoid present in large amounts in cranberries, is a potent downregulator of the nuclear factor (NF)-κB pathway [31]. In addition, quercetin has been shown to inhibit the activities of cyclooxygenase and lipoxygenase [31]. These enzymes are released after the stimulation of arachidonic acid, which is the initiator of a general inflammatory response. Furthermore, resveratrol, a polyphenol also present in cranberry juice, has been shown to decrease the expression of inflammatory genes relevant for cardiovascular disease by modulating the NF-κB and JAK STAT3 pathways in cultured cells [32].

The number of patients included in the study were small. Although the number of patients included in the study was small, the statistical power of the study was reached. Perhaps with a larger group it would be possible to observe significant differences in more parameters. Second, a placebo control group was not included, although a similar design has been previously used in several studies [33–36]. Third, we were not able to give detailed information about habitual intake. In general, Brazilian population intake is based on rice and beans, vegetables, and beef or chicken. The intake of food that could ameliorate symptoms of rheumatoid arthritis, especially fish (or fish oil) is negligible [37]. Therefore, habitual intake of the study population could hardly bias the results obtained in the present study, especially in terms of disease activity and inflammatory status. Nevertheless, the present study also has several strengths. First, to our knowledge, this is the first study to evaluate patients with RA using cranberry juice. Second, as only women were selected, a greater homogeneity in the results was obtained. Third, we rigorously tried to ensure that the patients did not take any drug or present any disease, which could interfere with the results. Fourth, although several features of DAS28, such as number of painful joints and global health evaluation, must be considered subjective, the decrease in anti-CCP levels verified in this study points out to an objective efficacy of cranberry juice on disease activity in patients with RA.

Conclusion

The hypothesis of beneficial effects with cranberry ingestion was partially confirmed by the decrease in disease activity in patients with RA. Nevertheless, there were no modifications in the inflammatory biomarkers. These findings may open new dietary supplemention opportunities for the management of RA, although this is probably the first study to investigate consumption of cranberries in patients with RA and larger, longer-term studies are needed to definitively probe this effect and to clarify the mechanisms involved. Thus, further research is needed to support the recommendation of cranberry consumption as a nutritional intervention for the treatment of rheumatoid arthritis. Also, studies are warranted to confirm these findings in male patients.

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