NATALY SIMÕES BANDIERA THIMOTEO

EFEITOS DA INGESTÃO DE SUCO DE CRANBERRY SOBRE BIOMARCADORES METABÓLICOS E INFLAMATÓRIOS NA SÍNDROME METABÓLICA E NA ARTRITE REUMATOIDE

Londrina
2018

NATALY SIMÕES BANDIERA THIMOTEO

EFEITOS DA INGESTÃO DE SUCO DE CRANBERRY SOBRE BIOMARCADORES METABÓLICOS E INFLAMATÓRIOS NA SÍNDROME METABÓLICA E NA ARTRITE REUMATOIDE

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Estadual de Londrina, como requisito parcial para a obtenção do Título de Doutor.

Orientador: Prof. Dr. Isaias Dichi

Londrina
2018

NATALY SIMÕES BANDIERA THIMOTEO

EFEITOS DA INGESTÃO DE SUCO DE CRANBERRY SOBRE BIOMARCADORES METABÓLICOS E INFLAMATÓRIOS NA SÍNDROME METABÓLICA E NA ARTRITE REUMATOIDE

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Estadual de Londrina, como requisito parcial para a obtenção do Título de Doutor.

BANCA EXAMINADORA

_____
Prof. Dr. Isaias Dichi - Orientador
Universidade Estadual de Londrina - UEL

_____
Profª. Elis Carolina de Souza Fatel
Universidade Estadual de Londrina - UEL

_____
Profª. Sayonara Rangel Oliveira
Universidade Estadual de Londrina - UEL

_____
Profa. Dra. Andréia Name Colado Simão
Universidade Estadual de Londrina - UEL

_____
Prof. Wander Bregano
Universidade Estadual de Londrina - UEL

_____
Profª. Marcell Alysson Batisti Lozovoy
Universidade Estadual de Londrina - UEL

Londrina, 27 de julho de 2018.

Dedico este trabalho e todo meu amor às minhas filhas Mariah e Laura, meu esposo Mário César, que estão sempre me inspirando a ser uma pessoa melhor, e aos meus pais a quem devo tudo que sou.

AGRADECIMENTOS

Agradeço primeiramente a Deus, pois sem Ele este sonho não se realizaria.

Agradeço ao meu esposo Mário César pela parceria, por todo apoio durante estes quatro anos para que eu pudesse concluir esta etapa. Agradeço às minhas filhas Mariah e Laura por terem trazido o real sentido à minha vida. Agradeço também aos meus pais pelos exemplos de pessoas que são, por me ensinarem a lutar pelos meus ideais e por todo incentivo ao estudo, que sempre me deram.

Agradeço à Universidade Estadual de Londrina pela oportunidade de obter mais uma formação, a todos os professores pela dedicação e aos colegas de curso por dividirmos juntos esta experiência. Gostaria de agradecer também a todos os colegas do grupo de pesquisa do Laboratório de Imunologia Aplicada que participaram diretamente ou indiretamente desse trabalho. Sem o apoio dessas pessoas, eu jamais conseguiria concluir esse projeto. "O segredo de um grande sucesso está no trabalho de uma grande equipe." (Autor desconhecido). Agradeço também ao CNPq pela bolsa de doutorado.

Agradeço a todos os pacientes do Ambulatório de Reumatologia do Hospital Universitário de Londrina pela participação no estudo. Espero que os conhecimentos adquiridos nesse trabalho possam contribuir de alguma forma para melhorar a qualidade de vida desses pacientes.

Enfim, gostaria de agradecer aos meus orientadores Dr. Isaias Dichi e Dra. Andréa Name Colado Simão por terem me aceitado como orientada, por toda a paciência que tiveram com todos os imprevistos surgidos durante estes quatro anos, e por todas as oportunidades e conselhos que me deram ao longo desta jornada. Com vocês pude partilhar de exemplos de dedicação, respeito, liderança e trabalho em equipe, fatores estes, contribuintes para a conduta ética e vencedora de vocês. Agradeço por crescer e aprender com vocês!

THIMOTEO, Nataly Simões Bandiera. **Efeitos da ingestão de suco de Cranberry sobre biomarcadores metabólicos e inflamatórios na síndrome metabólica e na artrite reumatoide.** 2018. 99f. Tese (Doutorado em Ciências da Saúde) – Universidade Estadual de Londrina, Londrina, 2018.

RESUMO

Introdução: O cranberry (*Vaccinium macrocarpon*), também conhecido como oxicoco ou arando-vermelho é um fruto nativo da América do Norte e constitui uma rica fonte de polifenóis, incluindo procianidinas, quercetina, miricitrina e antocianinas, fundamentais para a saúde cardiovascular. As propriedades antioxidantes destes frutos têm sido bem documentados em estudos em seres humanos e os efeitos cardiovasculares observados nesses estudos não se restringem apenas à capacidade antioxidante desses alimentos. Estudos com suplementação com cranberry mostraram benefícios em doenças metabólicas, como Síndrome Metabólica (SM) e autoimunes, como Artrite Reumatoide (AR). Assim, foi realizada uma revisão de literatura sobre os efeitos do cranberry nos parâmetros clínicos e laboratoriais da SM (artigo 1) e um artigo original para análise do consumo de suco de cranberry nos parâmetros clínicos e laboratorias em pacientes com AR (artigo 2). **Artigo 1:** Alguns estudos têm apontado para os benefícios do cranberry em perfis lipídicos, pressão arterial, função endotelial e uma variedade de biomarcadores de inflamação e estresse oxidativo. A SM é definida como um distúrbio complexo representado por uma combinação de fatores de risco cardiovascular tais como a obesidade central, dislipidemia, hipertensão e distúrbios no metabolismo da glicose, levando a um aumento do risco de doenças coronarianas, outros tipos de doenças cardiovasculares ateroscleróticas e diabetes do tipo dois (DT2). Assim, foi realizada uma revisão bibliográfica que reúne publicações recentes e/ou relevantes sobre o efeito do consumo de suco de cranberry nos parâmetros envolvidos na SM. **Artigo 2:** Estudo de intervenção que incluiu 41 pacientes do sexo feminino com AR. Os pacientes foram selecionados de acordo com critérios de classificação do Colégio Americano de Reumatologia/Liga Europeia contra o Reumatismo (ACR/EULAR). O primeiro grupo (n = 18) foi orientado a manter a sua dieta habitual; o segundo grupo (n = 23) recebeu 500 mL / dia de suco de cranberry de baixa caloria, sendo que três pacientes não completaram o estudo. O estado de atividade da doença foi determinado, por um médico reumatologista, utilizando o *Disease Activity Score 28 (*DAS28). Foram avaliados marcadores inflamatórios, tais como fator reumatóide (FR), velocidade de hemossedimentação (VHS), proteína C reativa (PCR), leucócitos e ferritina e marcadores bioquímicos, tais como HDL, LDL, colesterol total, triglicerídes, glicose, insulina, HOMA-IR e homocisteína, além do antipeptídeos citrulinados cíclicos (anti-CCP) como marcador de diagnóstico e prognóstico. Em relação aos valores basais, o grupo que consumiu suco de cranberry apresentou uma diminuição após os 90 dias de intervenção nos valores de DAS 28 (p=0,048) e anti-CCP (p=0,034). Contudo, não houve alterações significativas nos biomarcadores inflamatórios. Em conclusão, os resultados do artigo de revisão mostraram melhora em diversos parâmetros da SM, além de ter permitido melhor compreensão dos mecanismos fisiopatológicos envolvidos. A hipótese original subjacente ao estudo original, de que o suco de cranberry iria adicionar efeitos benéficos aos pacientes com AR foi confirmada mediante a diminuição da atividade

da doença e melhora do prognóstico, mediante a diminuição dos níveis de DAS 28 e do anti-ccp, respectivamente.

Palavras-chave: Artrite reumatoide. Síndrome metabólica. Cranberry. Inflamação. Estresse oxidativo.

THIMOTEO, Nataly Simões Bandiera. **Effects of Cranberry juice intake on metabolic and inflammatory biomarkers in metabolic syndrome and rheumatoid arthritis.** 2018. 99p. Thesis (Doctorate in Health Sciences) - Londrina State University, Londrina, 2018.

ABSTRACT

Introduction: Cranberry (Vaccinium macrocarpon), also known as cranberry or cranberry is a native fruit of North America and is a rich source of polyphenols, including procyanidins, quercetin, myricitrin and anthocyanins, which are essential for cardiovascular health. The antioxidant properties of these fruits have been well documented in studies in humans and the cardiovascular effects observed in these studies are not restricted only to the antioxidant capacity of these foods. Studies with cranberry supplementation have shown benefits in metabolic diseases such as Metabolic Syndrome (MS) and autoimmune diseases such as Rheumatoid Arthritis (RA). Thus, a review of the literature on the effects of cranberry on the clinical and laboratorial parameters of MS was carried out (article 1) and an original article for analysis of cranberry juice consumption in clinical and laboratory parameters in RA patients (article 2). **Article 1:** Some studies have pointed out to the benefits of cranberry in serum lipid profiles, blood pressure, endothelial function and a variety of biomarkers of inflammation and oxidative stress. Metabolic syndrome is defined as a complex disorder represented by a combination of cardiovascular risk factors such as central obesity, dyslipidemia, hypertension and disorders in glucose metabolism, leading to an increased risk of coronary heart disease, other types of atherosclerotic cardiovascular disease and type 2 diabetes (DT2). Thus, a bibliographical review was carried out that brings together recent and / or relevant publications on the effect of cranberry juice consumption on the parameters involved in the metabolic syndrome, as well as a summary of the pathophysiological mechanisms involved. **Article 2:** Intervention study that included 41 female patients with RA. Patients were selected according to the classification criteria of the American College of Rheumatology / European League against Rheumatism (ACR / EULAR). The first group (n = 18) was instructed to maintain their usual diet; the second group (n = 23) received 500 mL / day of low calorie cranberry juice, and three patients did not complete the study. Disease activity status was determined by a rheumatologist using Disease Activity Score 28 (DAS28). Inflammatory markers such as rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocytes and ferritin and biochemical markers such as HDL, LDL, total cholesterol, triglycerides, glucose, insulin, HOMA -IR and homocysteine, in addition to cyclic citrullinated antipeptides (anti-CCP) as diagnostic and prognostic marker. Regarding baseline values, the group that consumed cranberry juice showed a decrease after 90 days of intervention in the values of DAS 28 ($p = 0.048$) and anti-CCP ($p = 0.034$). However, there were no significant changes in inflammatory biomarkers. In conclusion, the results of the original article showed improvement in several parameters of MS, better understanding of the pathophysiological mechanisms involved. The original hypothesis underlying this study that cranberry juice would add beneficial effects to RA patients was confirmed by a decrease in disease activity and improvement of the prognosis, demonstrated by decreased DAS28 and anti-CCP levels, respectively.

Keywords: Rheumatoid arthritis. Metabolic syndrome. Cranberry. Inflammation. Oxidative stress.

LISTA DE ILUSTRAÇÕES

LISTA DE TABELAS

LISTA DE ABREVIATURAS

ACR	Colégio Americano de Reumatologia (*American College of Rheumatology*)
AEHU	Ambulatório de Reumatologia do Ambulatório de Especialidades do Hospital Universitário (*Ambulatory of Rheumatology of the Ambulatory of Specialties of the University Hospital)*
Anti-CCP	Anticorpo antipeptídeo citrulinado *(Anti-cyclic citrullinated peptide*)
APC	Célula apresentadora de antígeno (*Antigen-presenting cells*)
AR	Artrite Reumatoide (Rheumatoid arthitis)
ATP-III	Painel de Tratamento Adulto III (*Adult Treatment Panel III)*
CA	Circunferência abdominal *(Abdominal Circumference)*
DAS 28	Índice de atividade da doença (*Disease activity score 28)*
DCV	Doença cardiovascular *(Cardiovascular Disease)*
DM2	Diabetes Mellitus tipo 2 (*Type 2 Diabetes Mellitus)*
EDTA	Ácido etileno diamino tetra-acético (*Ethylenediamine tetraacetic acid*)
ELISA	Ensaio de imunoabsorção enzimática (*Enzyme-linked immunosorbent assay*)
ENOs	Óxido nítrico sintase endotelial (*Endotelial nitric oxide synthase*)
ERN	Espécies reativas de nitrogênio (*Nitrogen Reactive Species)*
ERRO	Espécies reativas de oxigênio (*Oxigen-Reactive Species)*
EULAR	Liga Europeia contra Reumatismo (*European League Against Rheumatism*)
FR	Fator Reumatóide (*Rheumatoid Factor)*
FRAP	Poder de redução do íon ferro (*Ferric Reducing Antioxidant Power*)
GSH	Glutationa (*Glutathione)*
HDL	Lipoproteína de alta densidade (*high density lipoprotein*)
HOMA	Avaliação do modelo homeostático (*Homeostatic Model Assessment*)

IMC	Índice de massa corporal (*Body Mass Index)*
LDL	*Lipoproteína de baixa densidade* (*Low Density Lipoprotein*)
MDA	Malondialdeído *(Malondialdehyde)*
MEIA	Imunoensaio em micropartículas (*Microparticle immunoassay)*
MTF	Metatarsofalangeanas (*Metatarsophalangeans)*
NCEP	Programa nacional de educação sobre o colesterol *(National Cholesterol Education Program)*
PCR	Proteína C-reativa *(C-reactive protein)*
SM	Síndrome Metabólica (*Metabolic Syndrome)*
TAS	Estado antioxidante total (*Total Antioxidant Status*)
TCLE	Termo de consentimento livre e esclarecido (*Free and informed consent form)*
TEAC	Capacidade Antioxidante Equivalente ao Trolox (*Trolox Equivalent antioxidant Capacity*)
TG	Triglicerídeos (*Triglycerides)*
TNF- α	Fator de necrose tumoral-α (*Tumor necrosis factor-α*)
UEL	Universidade Estadual de Londrina *(State University of Londrina)*
UV	Radiações Ultravioleta *(Ultraviolet Radiation)*

SUMÁRIO

1 INTRODUÇÃO

1.1 ARTRITE REUMATOIDE

O termo artrite reumatoide (AR), foi descrito há mais de 150 anos, para distinguí-la de outras formas de artrites, como reumatismo agudo e gota (GARROD, 1859). A AR é caracterizada pela destruição progressiva das articulações no corpo, sendo classificada, assim, como uma doença inflamatória sistêmica. A desordem provável resulta de indivíduos geneticamente suceptíveis a uma resposta imune anormal, com uma exposição ambiental específica. Esta é uma doença que afeta milhões de pessoas no mundo, e sua prevalência é de 1% (BROWN, 2007) e sua incidência varia entre 16,5 e 38 casos por 100.000 habitantes (MYASOEDOVA et al., 2010), sendo a estimativa de vida de pacientes com AR inferior a da população normal (GABRIEL et al., 2003; MINAUR et al., 2004). As mulheres são três vezes mais propensas a serem afetadas do que os homens (SPECTOR, 1990).

No longo prazo, as doenças músculo esqueléticas são as causas mais comuns de dores intensas, sendo esta uma condição que afeta significativamente o estado psicossocial do paciente, bem como de suas famílias e de seus cuidadores (WOOLF; AKESSON, 2001). Estas doenças acabam por utilizar uma quantidade considerável de recursos destinados a saúde. Em algum momento, 30% dos americanos adultos serão afetados por dor, edema ou limitações dos movimentos articulares (BJORKLUND, 1998).

1.1.1 Aspectos Clínicos e Laboratoriais na AR

Caracterizada como sendo uma doença sistêmica, a AR pode apresentar febre, fadiga, astenia, mialgia e perda ponderal, sintomas estes que podem anteceder ou acompanhar as manifestações articulares e extra-articulares (WOOLF, 2003). Na avaliação clínica, tem-se dor, inchaço, aumento do volume das articulações, derrame intra-articular, calor, e em alguns casos, rubor. Em articulações mais profundas, já não é tão evidente estas características, como nos quadris e ombros (WOOLF, 2003). A AR também pode ocasionar manifestações extra-articulares, dentre as mais frequentes pode-se observar quadros cutâneos, oculares, pleuropulmonares, cardíacos, hematológicos, neurológicos e osteometabólicos. Em pacientes com doença grave e poliarticulares, observa-se

sorologia positiva para fator reumatoide (FR) e anticorpos antipeptídeos citrulinados cíclicos (anti-CCP), juntamente com a presença de nódulos reumatoides (TURESSON et al., 2007; GOELDNER et al., 2011).

Para diagnóstico de AR, são utilizados os critérios classificatórios do *American College of Rheumatology* (ACR) / *European League Against Rheumatism* (EULAR) (ALETAHA et al., 2010), que consideram quatro parâmetros principais: número e tipo das articulações afetadas, presença de FR e/ou anti-CCP, proteínas de fase aguda (VHS e PCR) e duração dos sintomas (tabela 1).

Dentre as articulações mais acometidas, tem-se a metacarpofalangeanas (MCF), interfalangeanas proximais (IFP), metatarsofalangeanas (MTF), punhos, joelhos, cotovelos, tornozelos, quadris e ombros, em ordem decrescente de frequência, sendo as interfalangeanas distais (IFD) quase sempre poupadas. Com a doença já estabelecida, de forma mais tardia tem-se o acometimento simétrico e poliarticular (BURMESTER; POPE, 2017), sendo que qualquer articulação sinovial pode ser atingida.

Na avaliação laboratorial, os testes mais utilizados para avaliar a atividade da doença são as provas de atividade antiinflamatória dosagem da proteína C reativa (PCR) e velocidade de hemossedimentação (VHS) (DEVLIN, 1997). Mesmo sendo solicitados rotineiramente e tendo relação com o período de atividade da doença, estes testes não são específicos. A VHS e a PCR podem sofrer alterações de acordo com a idade e o sexo, e a VHS pode ser influenciada por diversos fatores, como níveis de hemoglobina, hipoalbuminemia, gravidez, hipofibrinogenemia, entre outras (DA MOTA; DOS SANTOS NETO; DE CARVALHO, 2009). Vale ressaltar que o diagnóstico da AR é caracterizado por achados clínicos e laboratoriais.

Tabela 1 - Critérios de classificação do ACR/EULAR 2010 para artrite reumatoide

População-alvo (quem deve ser testado?)	
Paciente com pelo menos uma articulação com sinovite clínica definida (edema). * Sinovite que não seja mais bem explicada por outra doença.	
*Os diagnósticos diferenciais podem incluir condições tais como lúpus eritematoso sistêmico, artrite psoriásica e gota. Se houver dúvidas quanto aos diagnósticos diferenciais relevantes, um reumatologista deve ser consultado.	
Envolvimento articular	
1 grande articulação	0
2-10 grandes articulações	1
1-3 pequenas articulações (com ou sem envolvimento de grandes articulações)	2
4-10 pequenas articulações (com ou sem envolvimento de grandes articulações)	3
10 articulações (pelo menos 1 pequena articulação)	5
Sorologia	
FR negativo e AACP negativos	0
FR positivo em título baixo ou AAPC positivo em título baixo	2
FR positivo em título alto ou AAPC positivo em título alto	3
Provas de fase aguda (pelo menos 1 é requerida)	
PCR normal e VHS normal	0
PCR anormal ou VHS anormal	1
Duração dos sintomas	
< 6 semanas	0
≥ 6 semanas	1

Pontuação maior ou igual a 6 é necessária para classificação definitiva de um paciente como AR. O domínio acometimento articular refere-se a qualquer articulação dolorosa ou inchada (excluindo interfalangeanas distais do pé ou da mão, primeira metatarsofalangeana e primeira carpometacarpeana). Evidência adicional obtida por exames de imagem pode ser utilizada para confirmação dos achados clínicos. Consideram-se, para fins de classificação, como pequenas articulações as metacarpofalangeanas, interfalangeanas proximais, metatarsofalangeanas (segunda a quinta), primeira interfalangeana e punhos, e como grandes articulações ombros, cotovelos, quadril, joelhos, tornozelos. Articulações adicionais (temporomandibular, esternoclavicular, acromioclavicular, entre outras) podem ser contadas, na avaliação de “mais de 10 articulações”, desde que uma pequena articulação (ao menos) esteja acometida.

No domínio sorologia, considera-se o resultado de fator reumatoide ou de anticorpos anti-peptídeos/proteínas citrulinadas negativo se o valor encontrado for igual ou menor ao limite superior da normalidade para o respectivo laboratório; positivo baixo se o valor encontrado for maior que o limite superior da normalidade, mas menor ou igual a três vezes o limite superior da normalidade; e positivo alto quando o valor encontrado for superior a três vezes o limite superior da normalidade.

O domínio duração dos sintomas se refere ao relato do próprio paciente quanto à duração máxima dos sinais e sintomas de qualquer articulação que esteja clinicamente envolvida no momento da avaliação.

Já as provas de atividade inflamatória (velocidade de hemossedimentação e proteína C reativa) são consideradas normais ou anormais de acordo com o valor de referência do laboratório utilizado.

ACPA: *anti-citrullinated protein antibodies*; ACR: *American College of Rheumatology*; EULAR: *European League Against Rheumatism;* FR: fator reumatoide; PCR: proteína C reativa; VHS: velocidade de hemossedimentação

Fonte: Modificado de Aletaha et al. (2010)

Estes novos critérios ACR/EULAR podem ser utilizados para todos os indivíduos com AR que cumpram dois requisitos básicos: presença de sinovite

clínica em pelo menos uma articulação no momento do exame e em pacientes cuja a sinovite não possa ser melhor explicada por outro diagnóstico (MOTA et al., 2011).

Vale ressaltar que se o paciente apresentar um histórico compatível com AR e erosões radiográficas características, independente do preenchimento do critério ele pode ser classificado como portador de AR (ALETAHA et al., 2010).

Como parâmetros para monitoramento da atividade da doença, podemos relacionar escalas visuais de dores do paciente, atividade da doença pelo paciente e pelo médico, métodos de avaliação da capacidade funcional (como o HAQ-*Healt Assessment Questionnaire*), quantidade de articulações dolorosas e edemaciadas, fadiga, tempo de rigidez matinal, índice de qualidade de vida, e radiografia de mãos, punhos e pés (TUGWELL; BOMBARDIER, 1982; SCOTT et al., 1992; VAN DER HEIJDE et al., 1992; FELSON et al., 1993; GOLDSMITH et al., 1993; BOERS et al., 1994).

O índice *Disease Activity Score* 28 (DAS 28) é utilizado de forma confiável em ensaios clínicos e outras análises e tornou-se um padrão para uso na prática clínica e ensaios clínicos. Baseado na contagem de 28 articulações (IFP, MCF, punhos, cotovelos, ombros e joelhos, bilateralmente) foi estabelecido um valor numérico para atividade da AR (tabela 2) (PREVOO et al., 1995). Esse valor numérico é calculado pela fórmula matemática: $0,56 \times \sqrt{NAD28} + 0,28 \times \sqrt{NAE28} + 0,70 \times Ln\ VHS + 0,014 \times AGS$, onde NAD28 é o número de articulações dolorosas dentre 28 pré determinadas, NAE28 é o número de articulações edemaciadas dentre 28 articulações pré determinadas, Ln é o logaritmo e AGS é avaliação global de saúde. Sendo que o cálculo pode ser feito de forma prática através de calculadoras disponíveis na internet (www.das-score.nl) ou por aplicativos de celulares.

Tabela 2 - Classificação da Atividade da Doença de Acordo com os Critérios Propostos pelo *Disease Activity Score 28* (DAS 28)

Estado de atividade	DAS28
Remissão	≤2,6
Baixa	≤3,2
Moderada	≤5,1
Alta	>5,1

Fonte: Prevoo (1995)

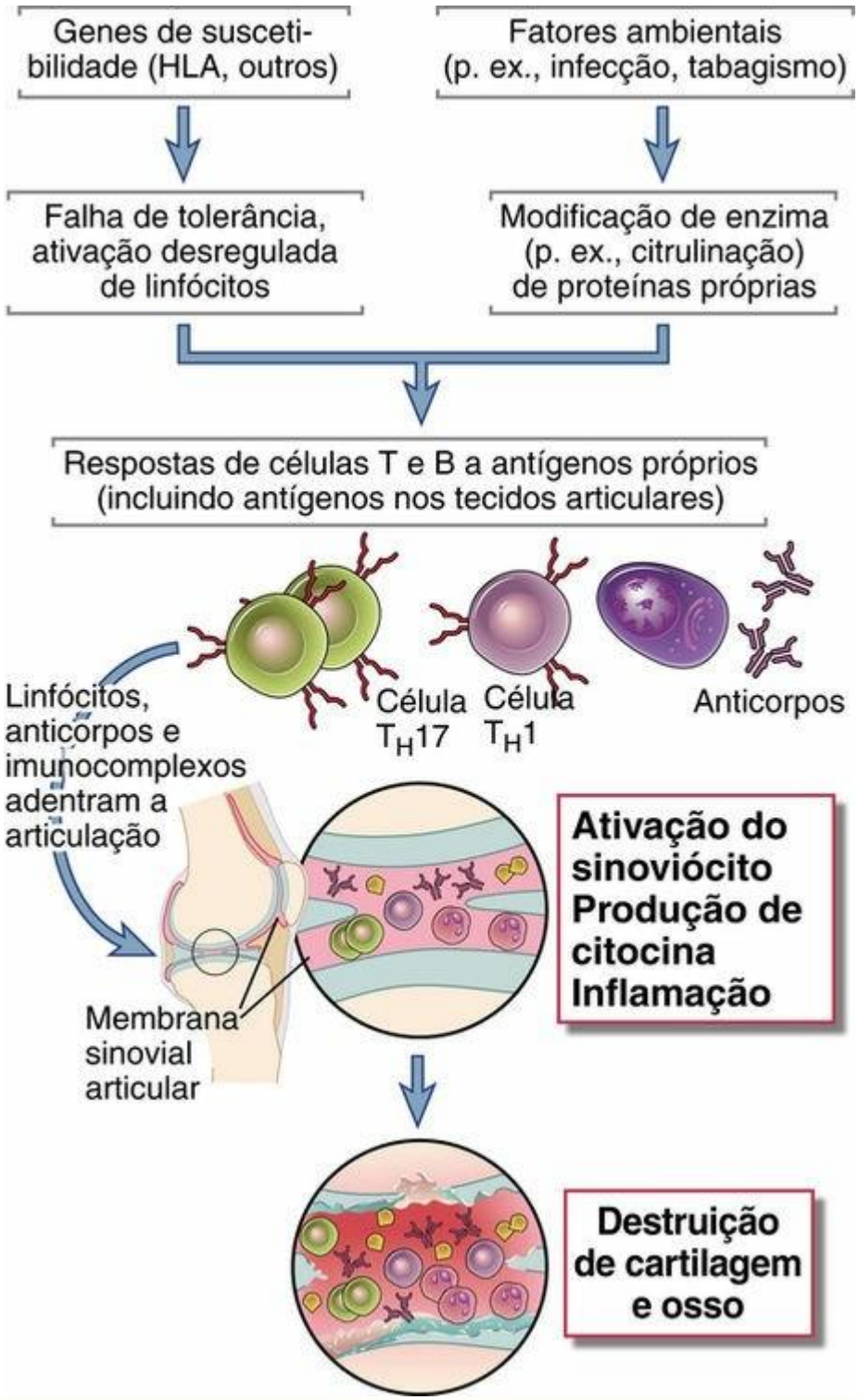
1.2 INFLAMAÇÃO E ARTRITE REUMATOIDE

Pacientes com AR apresentam inflamação e destruição articular como características principais, além de várias comorbidades associadas, sendo que as citocinas desempenham um importante papel neste processo. Eles apresentam células B e T ativadas na membrana sinovial, estruturas com arranjo semelhantes a do centro germinativo, como células plasmáticas, mastócitos e macrófagos ativados, praticamente todos com linfangiogenese associada, sendo selecionados por meio de neovascularização intensa. No hospedeiro, as células (fibroblastos sinoviais, condrócitos e osteoclastos) são envolvidas para manter a continuidade do processo inflamatório e a detruição do osso, sendo que todo este processo é conduzido por uma rede de citocinas (BRENNAN; MCINNES, 2008) (figura 1).

Pode-se considerar alguns anticorpos como potenciais marcadores de AR, como o FR e diversos anticorpos antiproteínas, por exemplo, o anti-CCP (VISSER, 2005). A auto-imunidade e o fator de inflamação sistêmico e articular ocasionam a progressão destrutiva da doença. As modificações nas estruturas podem ser observadas por radiografia convencional ou outras técnicas de imagem, distinguindo assim, de uma melhor maneira a AR de outras doenças artríticas (BOHNDORF, 1996). O dano nas articulações dificilmente é observado nos estágios iniciais da doença, mas se torna aparente com o passar do tempo (VAN DER HEIJDE, 1995; PLANT et al., 1998; WOLFE; SHARP, 1998; MACHOLD, 2002).

Até o momento, não se sabe qual é o agente etiológico da AR, mas atualmente, a hipótese aceita é de que um desencadeador ambiental (tabagismo, bactéria ou partículas de sílica ou poeira) entraria por uma mucosa (pulmões, gengiva ou intestino) provocando uma resposta imune celular inata, ativando neutrófilos, células dendríticas imaturas e macrófagos, que irão gerar o início da inflamação e produção de autoantígenos, como as proteínas citrulinadas**.** Desta forma, sendo ativadas, as células apresentadoras de antígenos (APC) irão processar e apresentar os antígenos citrulinados para as células T, e que por sua vez ativam as células B, levando a produção de autoanticorpos (CATRINA et al., 2016). Assim, com o passar do tempo, aumentam a concentração e a diversidade de epítopos dos autoanticorpos contra peptídeos citrulinados, da mesma forma que as concentrações séricas de citocinas, especialmente antes do início do envolvimento articular (SMOLEN; ALETAHA; MCINNES, 2016).

Figura 1: Patogênese da AR associada à inflamação



De acordo com esse modelo, as proteínas citrulinadas induzidas por estímulos ambientais produzem respostas de células T e de anticorpos em indivíduos geneticamente suscetíveis. As células T e os anticorpos adentram articulações, respondem a proteínas próprias e causam lesão tecidual principalmente por secreção de citocinas e, talvez, também por mecanismos efetores dependentes de anticorpos. Outras modificações de proteínas além da citrulinação podem levar ao mesmo resultado.

Fonte: ABBAS; LICHTMAN; PILLAI (2015). Disponível em: http://www.conteudoacademicoweb.com.br/2017/10/capitulo-19-reacoes-de.html. Acesso em 14 de junho de 2018.

A AR, é uma doença caracterizada por alto nível de estresse oxidativo, bem como inflamação local e sistêmica, com aumento das concentrações plasmáticas de citoquinas pró-inflamatórias, como Fator de necrose tumoral-α (TNF-α) , interleucina 1-β (IL-β) e interleucina-6 (IL-6) (RENNIE et al., 2003; COLEMAN, 2005; CHIMENT et al., 2015).

Na presença de lesões articulares, a membrana sinovial apresenta infiltrado de linfócitos T, macrófagos e plasmócitos secretores de anticorpos. Existe ainda a proliferação de sinoviócitos. Novos vasos sanguíneos, juntamente com estas células dão a origem a um tecido, o pannus, que ocasiona a destruição progressiva do osso e da cartilagem. Este mecanismo acontece através da indução de enzimas, tais como a metaloproteínases mediadas por eicosanóides e citocinas. O TNF-α, IL-β, IL-6 e IL-8, bem como fator estimulante de macrófagos/granulócitos, que são citocinas pró-inflamatórias presentes no líquido sinovial de indivíduos com AR, em níveis elevados (MILES; CALDER, 2012).

O aumento do estresse inflamatório e oxidativo desempenha um papel notável na iniciação e progressão da doença vascular aterosclerótica (TOSHIMA et al., 2000; LIBBY; RIDKER; MASERI, 2002). Como exemplo, a liproteína de baixa densidade oxidada (ox-LDL) é um marcador de estresse oxidativo, está aumentada em indivíduos com doenças cardíacas coronarianas (TOSHIMA et al., 2000) e é considerada um marcador de progressão da aterosclerose subclínica (WALLENFELDT et al., 2004). Além disso, o aumento de citocinas pró-inflamatórias, incluindo o TNF- α (RIDKER et al., 2000), IL-6 (RIDKER et al., 1998), interleucina 18 (IL-18) (BLANKEMBERG et al., 2003) e PCR (KOENIG et al., 1999) é considerado marcador de inflamação sistêmica e indicador de eventos ateroscleróticos futuros.

Desta forma, a síndrome metabólica (SM) é definida como um conjunto de distúrbios cardiometabólicos resultantes do aumento da obesidade. Dentre os principais componentes da SM, temos resistência à insulina, obesidade central, hipertensão e dislipidemia, aumentando assim o risco de doenças cardivasculares e de diabetes mellitus tipo 2 (DM2). De acordo com estudos realizados, é sugestivo que o estado pró-inflamatório e o estresse oxidativo na AR podem auxiliar no desenvolvimento da SM (BORGES et al., 2007; CHUNG et al., 2008). Assim, a probabilidade de doenças cardiovasculares se torna maior em pacientes com doenças reumáticas, tais como AR (PICERNO et al., 2015; SKEOCH; BRUCE, 2015; NAKAJIMA, 2016).

1.3 ESTRESSE OXIDATIVO E NITROSATIVO NA ARTRITE REUMATÓIDE

O equilíbrio redox é importante para um perfeito funcionamento das funções vitais celulares (VALKO; LEIBFRITZ; MONCOL, 2007), sendo o EO definido como o desequilíbrio nas características redox no ambiente celular. O EO pode ser gerado pelo resultado de processos bioquímicos que levam a produção de espécies reativas, devido à exposição a agentes prejudiciais (ou seja, meio ambiente e radiação), ou ainda capacidade antioxidante limitada do sistema endógeno (FRANCO et al., 2009; HODJAT; REZVANFAR; ABDOLLAHI, 2015).

Como subproduto do metabolismo celular, têm-se diversas espécies reativas de oxigênio (ERO) e de nitrogênio (ERN). Estas reagem agilmente com outras moléculas ou radicais, provocando a oxidação seletiva de moléculas de lipídeos, proteínas e DNA (KALYANARAMAN, 2013). Radicais livres e metabólitos reativos, também conhecidos como ERO / ERN, são produtos normais do metabolismo celular e são gerados principalmente pela cadeia respiratória mitocondrial. Quando há um desequilíbrio entre a produção destas espécies reativas e a sua eliminação por mecanismos antioxidantes, ocorre um acúmulo de ERO, levando ao EO. A inflamação crônica pode ser resultado do EO contínuo (REUTER et al., 2010).

Os oxidantes são estímulos para a produção de ERO dentro da célula; dentre eles podemos citar infecções, radiações ultravioleta (UV) e poluentes. As ERO também consideradas fatores de risco e aceleradores de doenças autoimunes (AVALOS et al., 2007), levando-se em conta a ligação existente entre o EO e estas doenças (SURH, 2005).

As ERO participam na defesa frente a microrganismos invasores e está relacionada com várias funções fisiológicas. Elas auxiliam na manutenção do estado celular redox e são produzidas no metabolismo celular aeróbico normal (SURH, 2005; OKTYABRSKY; SMIRNOVA, 2007). De forma endógena, temos diversos sistemas no corpo humano que agem para contrabalançar as ERO e manter um equilíbrio redox adequado (WANG et al., 2010; ERSA et al., 2012). Estes antioxidantes são nomeados como enzimáticos, como superóxido dismutase, catalase e glutationa peroxidase, e não enzimáticos, como vitaminas C e E, ácido úrico e glutationa (GSH) que é o principal antioxidante não enzimático em células humanas (ERSA et al., 2012). Os sistemas antioxidantes não enzimáticos têm

origem extracelular enquanto os antioxidantes enzimáticos e a glutationa são predominantemente encontrados no meio intracelular (VASCONCELOS et al., 2007).

O estado redox em desequilíbrio traz efeitos deletérios nas biomoléculas sobre a biologia celular. Devido a isto, existem vários mecanismos antioxidantes participantes na proteção de células e organismos para um eventual dano provocado pelo grande aumento desses mediadores altamente reativos (BLAIR, 2006; SONEJA; DREWS; MALINSK, 2005).

Em estudo que comparou indivíduos com AR e indivíduos saudáveis, a produção mitocondrial de ERO em sangue total e monócitos com AR se encontrava cinco vezes maior (MIESEL; MURPHY; KRÖGER, 1996). Um dos fatores que contribui para a aterosclerose, que ocorre de forma acelerada na AR, é a peroxidação lipídica. Na AR, a inflamação local e sistêmica persistente resulta em lipólise, com consequente liberação sistêmica de ácidos graxos que contribui para a dislipidemia encontrada na AR. O EO produzido na inflamação local leva a oxidação do LDL local, o que ocasiona o aumento das moléculas de adesão e citocinas (HITCHON; EL-GABALAWY, 2004).

Já é conhecido que as ERO estão envolvidos na patogenese da AR (BIEMOND; SWAAK; KOSTER,1984). Durante processos oxidativos, que ocorrem em todas as células e tecidos, temos a formação do ERO. Em condições naturais, uma variedade de antioxidantes serve para controlar a produção de ERO. Em contrapartida, altas concentrações e/ou remoção inadequada de ERO ocasionam EO, o que pode provocar graves disfunções metabólicas e danos biológicos em macromoléculas (HALLIWELL; GUTTERIDGE, 1996). Além disso, a decomposição de peróxido de lipídeo produz uma grande variedade de produtos finais, entre eles malondialdeído (MDA). Assim, no soro ou plasma de pacientes com AR, observam-se níveis elevados de MDA (BIEMOND; SWAAK; KOSTER, 1984; GAMBHIR et al., 1997; CIMEN et al., 2000; OSTRAKHOVITCH; AFANASEV, 2001). A reação em cadeia destrutiva iniciada pela ERO, pode ser substituída por substratos inofensivos, através da ação de antioxidantes (HALLIWELL; GUTTERIDGE, 1996).

1.4 FATORES DE RISCOS CARDIOVASCULAR E SÍNDROME METABÓLICA NA ARTRITE REUMATÓIDE

A SM é definida como sendo uma soma de vários achados clínicos e laboratoriais em pacientes: obesidade abdominal, resistência à insulina (glicose em jejum elevada), hipertensão, dislipidemia (diminuição do nível de HDL e aumento dos triglicerídeos) (REAVEN, 1993). Em comparação com a população em geral, a SM é responsável por um aumento de três vezes no risco de DCV, aumento da mortalidade por DCV (FORD, 2005) e um risco quatro vezes maior de desenvolvimento de DM 2 (HANLEY et al., 2005).

Há vários critérios diagnósticos de SM, sendo a do *National Cholesterol Education Program* (NCEP) *Adult Treatment Panel III* (ATP III) a mais utilizada.Ela considera a presença de pelo menos três dos componentes presentes na figura 2 para o seu diagnóstico.

Figura 2: Critérios para identificação da SM:

Obesidade abdominal (perímetro da cintura)	
Homem	> 102 cm
Mulher	> 88 cm
Triglicerídeos	≥ 150 mg/dl
HDL Colesterol	
Homem	< 40 mg/dl
Mulher	< 50mg/dl
Pressão Arterial	≥ 130/85 mm Hg
Glicemia em jejum	≥ 110 mg/dl

Fonte: Penteado, Gomes (2008)

O aumento de marcadores circulantes de EO e inflamação de baixo grau estão associados à obesidade (FESTA et al., 2001). A SM que frequentemente é acompanhada de obesidade, também foi relacionada com ao aumento do processo inflamatório e EO (HANSEL et al., 2004; FESTA et al., 2000). Vale ressaltar, que o risco de DCV é consideravelmente maior em indivíduos obesos com SM em comparação com aqueles sem SM (LAKKA et al., 2002).

A SM é altamente prevalente (FORD; GILES; GIETZ, 2002), e os indivíduos afetados possuem alto risco cardiovascular de morbidade e mortalidade (ISOMAA et al., 2001). Além disso, a SM é um forte preditor na incidência de DM 2 (LORENZO et al., 2003; LAAKSONEN et al., 2002; HANSON et al., 2002; RESNICK et al., 2003),

esta última sendo importante fator de risco de DCV. As principais características da SM, incluindo inflamação e aumento do estresse oxidativo podem sofrer alterações através de intervenções alimentares envolvendo alimentos e bebidas ricas em polifenóis, como soja (AZADBAKHT et al., 2007), bagas (EULUND et al., 2008) e chá verde (BASU et al., 2010). Por esse motivo, a SM tem sido alvo de dietas e terapias farmacológicas (ALBERTI et al., 2009).

Todos parâmetros da SM que incluem resistência à ação da insulina / DM 2, hipertensão, dislipidemia e obesidade central podem aumentar, mesmo individualmente, o estresse oxidativo (CERIELLO; QUATRARO; GIUGLIANO, 1993; GIUGLIANO; CERIELLO; PAOLISSO, 1995; WEST, 2000) e diminuir a defesa antioxidante (ANTONIADES et al., 2003; STOCKER; KEANEY, 2004; PENCKOFER; SCHWERTZ; FLOREZAK, 2002). A elevação do estresse oxidativo promove a inflamação, disfunção endotelial, trombose, aterosclerose, dando origem a doenças vascular aterosclerótica (GIUGLIANO, 2000) .

As manifestações bioquímicas e o desenvolvimento clínico da SM, podem ser gerados pelo estado sistêmico pró-inflamatório de baixo grau (DANDONA et al., 2005). Em estudos clínicos, os níveis de proteína C reativa (PCR) de alta sensibilidade e a IL-6 são frequentemente usadas como marcadores inflamatórios que favorecem os estágios iniciais da doença arterial coronariana (LUC et al., 2003). A IL-6 é uma citocina pró-inflamatória mensageira, que é secretada por macrófagos e células musculares lisas em lesões ateroscleróticas, enquanto a PCR é um produto de inflamação hepática e está sob a regulação de IL-6 (HEINRICH; CASTELL; ANDUS, 1990; BATAILLE; KLEIN, 1992). Em indivíduos normais, a adiponectina é secretada em abundância pelos adipócitos, sendo conhecida por ser um marcador anti-inflamatório potencialmente antiaterogênico (DANDONA et al., 2005; MATSUZAWA et al., 2004), e que se encontra diminuída na SM. Estudos clínicos sugerem que a inflamação de baixo grau tem um papel importante na fisiopatologia da SM (DAS, 2004; CHOI et al., 2007).

Scrivo et al. (2013) demonstraram que a prevalência de obesidade estava associada com o aumento da incidência e gravidade de AR. Além disso, Crowson et al. (2013) sugeriram que a crescente prevalência da obesidade poderia ser responsável por grande parte do aumento da incidência de AR. Confirmando esta última hipótese, um estudo de meta-análise mostrou que um aumento no índice de massa corporal (IMC) contribuía para um maior risco de desenvolvimento de AR

(QIN et al., 2015). Recentemente, um estudo demostrou que os pacientes com AR com diagnóstico de obesidade tinham parâmetros de maior atividade da doença (ELLABBAN et al., 2016).

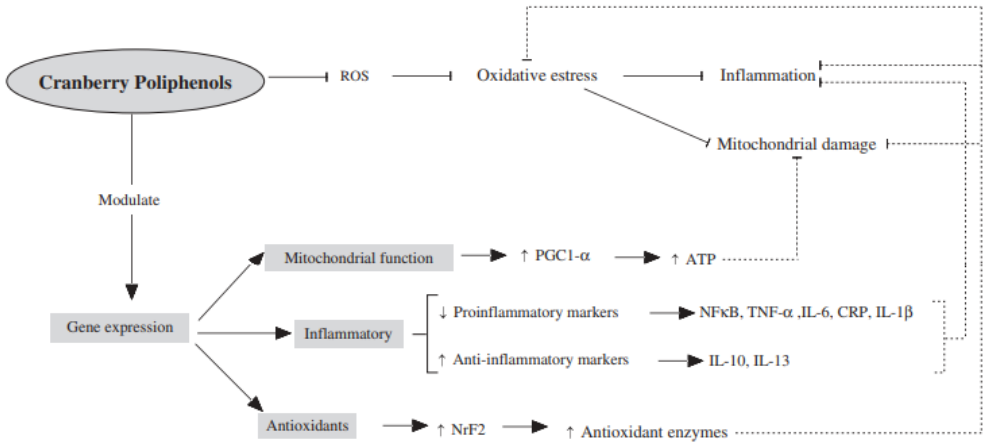
Atualmente, estudos evidenciam que pode existir uma interação entre alteração de secreção de adipocinas pró-inflamatórias presentes na obesidade e na SM com as doenças cardiovasculares e doenças reumáticas (ABELLA et al., 2014) e que as manifestações clínicas que estão presentes na SM devem ser monitoradas, durante o curso da AR (KEREKES et al., 2014). A intervenção nutricional na AR e na SM propiciada por algum tipo de nutriente, estaria indicado e poderia beneficiar ambas as doenças. Isso, poderia ser o caso de nutriente rico em flavonóides, como é o caso do cranberry.

1.5 CRANBERRY

O cranberry (V*accinium macrocarpon*) é uma planta cultivada na América do Norte desde o início do século XIX, tendo sua origem no Canadá e nos Estados Unidos (MARCHAND et al., 2013). Inicialmente, o cranberry foi usado por índios para tratar infecções do trato urinário (GUAY, 2009; MARCHAND et al., 2013). Este fruto também era utilizado para tratar de feridas, indigestões, higiene oral e dentária, pedras nos rins e outros problemas urinários, entre os nativos norte-americanos (DUTHIE et al., 2005; DESSÌ; ATZEI; FANOS, 2011). Analisando a composição do cranberry, pode-se encontrar flavonoides, catequinas, triterpenóides, ácidos orgânicos, vitaminas (A e C), carboidratos, sais minerais e taninos tais como as proantocianidinas (DESSÌ; ATZEI; FANOS, 2011). Podendo seu consumo ser em frutas secas, molhos ou suco (MARCHAND et al., 2013).

O cranberry (*Vaccinium macrocarpon*), também conhecido como oxicoco ou arando-vermelho é um fruto nativo da América do Norte e constitui uma rica fonte de polifenóis, incluindo procianidinas, quercetina, miricitrina, ácido elágico e antocianinas, fundamentais para a saúde cardiovasculares e trato urinário (VATTEM; GHAEDIAN; SHETTY, 2005; RUEL et al., 2006; NETO, 2007; KIM et al., 2008; RUEL et al., 2008; WING et al., 2008; DOHADWALA et al., 2011; BASU et al., 2011). Os mecanismos anti-oxidantes e antiinflamatórios do cranberry estão representados na figura 3.

Figura 3: Mecanismos anti-oxidantes e antiinflamatórios do Cranberry



Fonte: CALDAS; COELHO; BRESSAN (2018)

No Brasil, o cranberry pode ser consumido na forma de suco industrializado, polpa da fruta congelada ou cápsulas. Recentemente, vem sendo reconhecido como um alimento funcional e nutracêutico, por possuir um grande número de substâncias biologicamente ativas. Destaca-se também como uma importante fonte de vitaminas, como o ácido ascórbico; seu teor no cranberry é, em média, 10 mg/100 g matéria seca (MS), cerca de 21% menor do que em arandos silvestres (DOROFEJEVA et al., 2011). No fruto fresco, avaliou-se que o teor atingiu cerca de 134 mg/100 g MS. Esta vitamina também pode estar presente em grande quantidade no suco de cranberry, 897 mg/L, sendo esta a maior fonte de consumo no produto (DUTHIE et al., 2006).

O suco de cranberry apresenta a mesma quantidade de resveratrol que o suco de uva (WANG et al., 2002), sendo que pode-se relacionar os benefícios do resveratrol com a saúde cardiovascular, eliminação de espécies reativas de oxigênios, inibição da agregação plaquetária e diminuição da inflamação (RUEL, 2007).

Atualmente, o número de estudos avaliando a função do cranberry nos fatores de riscos cardiometabólicos vêm crescendo. Alguns estudos têm apontado para os benefícios do cranberry em perfis lipídicos, pressão arterial, função endotelial e uma variedade de biomarcadores de inflamação e estresse oxidativo (BLUMBERG et al., 2016).

1.5.1 Cranberry e Risco Cardiovascular

De acordo com estudos observacionais e de intervenção, o consumo de cranberry pode ser associado a efeitos benéficos sobre SM, afetando um ou mais de seus componentes (RUEL et al., 2009, SIMÃO et al., 2013). Os mecanismos fisiológicos e moleculares envolvidos não são completamente compreendidos, mas estão relacionados principalmente à sua capacidade antioxidante, capacidade de modulação enzimática e regulação da expressão gênica (MCKAY; BLUMBERG, 2007).

Um estudo duplo-cego com placebo, utilizando 58 pacientes ingerindo 240ml/2x por dia de suco de cranberry de baixa caloria, por um período de 8 semanas. Observou-se uma melhora relevante em vários fatores de riscos envolvidos em DCV, tais como glicose, resistência à insulina, PCR, triglicerídeos séricos e pressão arterial diastólica (NOVOTNY et al., 2015).

Assim, o consumo de suco de cranberry tem sido associado à diminuição dos biomarcadores do risco de DCV como descrito em estudos clínicos. Em voluntários saudáveis, após o consumo de suco de cranberry, demonstrou-se aumento da capacidade antioxidante no plasma (PEDERSEN et al., 2000). Ensaios de intervenção, com ou sem placebo, variando de 2 a 16 semanas, demonstraram que o uso de cranberry em voluntários saudáveis, ocasionava uma melhora no estresse oxidativo, na resposta glicêmica pós-prandial, na dislipidemia e em marcadores ateroscleróticos (RUEL et al., 2005; RUEL et al., 2006; RUEL et al., 2008) em pacientes com diabetes méllitus tipo 2 (CHAMBERS; CAMIRE, 2003; LEE et al., 2008). Além disso, foram realizadas duas intervenções de 12 semanas em pacientes diabéticos tipo 2, que consumiram pó concentrado de suco de cranberry ou pó de extrato de cranberry com diminuição significativa na insulina sérica (CHAMBERS; CAMIRE, 2003) e nos níveis de colesterol total (LEE et al., 2008), respectivamente. Em contraste, um estudo com mulheres saudáveis com duração de duas semanas não resultou em alterações destas substâncias no sangue, no estado antioxidante celular, em biomarcardores de riscos de DCV e no risco de câncer, após o consumo de suco de cranberry versus a intervenção com placebo (DUTHIE et al., 2006).

Nosso grupo de estudos (SIMÃO et al., 2013), analisou o efeito da ingestão de suco de cranberry de baixa caloria em biomarcadores metabólicos e inflamatórios em pacientes com SM. Verificou-se que após 8 semanas de consumo de 700 ml de

suco/dia foi observado um aumento significativo nos níveis de adiponectina e de ácido fólico, redução da homocisteína e dos níveis de lipoperoxidação e oxidação de proteínas, porém não foram observadas alterações significativas nas citocinas pró-inflamatórias TNF-α, lL-1 e IL-6. Assim, foi concluído que o consumo do suco de cranberry contribuiu na melhora de vários fatores de risco cardiovasculares (SIMÃO et al., 2013).

1.5.2 Cranberry e Artrite Reumatoide

O objetivo do tratamento dos pacientes com AR é o de prevenir e controlar a perda da função articular e o dano ósseo, e diminuir a dor, prevenir a incapacidade funcional e melhorar a qualidade de vida deste paciente (BÉRTOLO et al., 2009; MOTA et al., 2011).

Cranberries como frutas secas ou sumos foram classificados como tendo alta capacidade antioxidante, quando comparados com damascos, figos, ameixas e passas, bem como com bebidas ricas em polifenóis, como chá verde e vinho tinto (VINSON et al., 2008). As substâncias antioxidantes são nutrientes que, em baixa concentração, minimizam ou retardam a oxidação de substratos oxidáveis (HALLIWELL et al., 1995). Entre os antioxidantes não enzimáticos responsáveis pela redução molecular e celular no estresse oxidativo, merecem atenção especial a vitamina A, C, E, zinco e selênio (BERGER, 2005).

Com a evolução na pesquisa clínica, pode ser constatado uma associação entre a ingestão de nutrientes antioxidantes e a diminuição na formação de radicais livres, assim como em aspectos relacionados a patogenêse da doença (RICCIONE et al., 2007), demonstrando que estes antioxidantes suprimem de forma efetiva a liberação de citocinas inflamatórias, diminuindo assim ERO (SURH et al., 2005) e apresentando efeito protetor no desenvolvimento da AR (PATTISON; HARRISON; SYMMONS, 2004).

O consumo de suco de cranberry por adultos pode ser responsável pela melhora de vários fatores de risco de doenças cardiovasculares, incluindo triglicerídos circulantes, PCR, glicose, resistência à insulina e pressão arterial diastólica (NOVOTNY et al., 2015). A ingestão de polifenóis, presentes no cranberry, pode ter um papel significativo na promoção de marcadores anti-inflamatórios entre os consumidores do suco de cranberry, pois através de uma pesquisa recente foi

identificado que os consumidores deste suco apresentaram níveis de PCR significativamente mais baixos que os não consumidores (DUFFEY; SUTHERLAND, 2015).

Recentemente, uma outra pesquisa avaliou a composição do cranberry e seus efeitos na produção de citocinas, sendo demonstrado que o mesmo possuiu capacidade de inibir IL-6, IL-8 e o fator de crescimento endotelial vascular, inibindo assim a IL-1β (TIPTON; CHRISTIAN; BLUMER, 2016).

2 JUSTIFICATIVA

Considerando:

1) Os efeitos benéficos, como antioxidantes e antinflamatórios do consumo do cranberry;

2) A alta prevalência de artrite reumatoide e seus efeitos deletérios na qualidade de vida do paciente;

3) Os artigos que verificaram o benefício do cranberry em doenças com baixo grau de atividade anti-inflamatória, como a SM;

4) A inexistência de artigos que tenham verificado os efeitos do cranberry sobre esta doença , este artigo original tem por objetivos:

3 OBJETIVOS

3.1 OBJETIVO GERAL

Avaliar o efeito do consumo de suco de cranberry de baixa caloria sobre a atividade da doença, biomarcadores inflamatórios e metabólicos em pacientes com AR, após 90 dias. Assim como realizar uma revisão, sobre os principais estudos de intervenção em humanos envolvendo o consumo de cranberry e os componentes da SM, além de resumir os mecanismos mais relevantes envolvidos.

3.2 OBJETIVOS ESPECÍFICOS

a) Avaliar os efeitos do consumo do suco de cranberry na atividade da AR por meio do DAS 28
b) Avaliar os efeitos do consumo do suco de cranberry sobre os marcadores biometabólicos, tais como perfil lipídico e o metabolismo da glicose em pacientes com AR;
c) Avaliar os efeitos do consumo do suco de cranberry sobre os marcadores inflamatórios e imunológicos, como leucócitos, PCR, VHS, FR, anti-ccp, ferritina e homocisteína;
d) Realizar uma revisão de literatura sobre os efeitos do consumo de cranberry nos componentes metabólicos e inflamatórios da SM.

4 MATERIAIS E MÉTODOS

4.1 REVISÃO DE LITERATURA

Para a revisão da literatura foram utilizadas as seguintes bases de dados: *U.S. National Library of Medicine PUBMED*, *Science Direct*, e *Scientific Electronic Library Online*. A pesquisa foi realizada sem limite de tempo e o idioma utilizado foi o inglês. Foram utilizadas como palavras-chave cranberry, metabolic syndrome, obesity, hypertension, dyslipidemia, cardiovascular risk markers, oxidative stress, glucose metabolismo, inflammatory markers.

4.2 POPULAÇÃO, AMOSTRA E DELINEAMENTO

No total, 41 mulheres foram selecionadas para participar do estudo, entre pacientes atendidos no Ambulatório de Reumatologia do Ambulatório de Especialidades do Hospital Universitário (AEHU) da Universidade Estadual de Londrina (UEL) e voluntários do Hospital Universitário da UEL, Londrina, Paraná. Esse é um ensaio clínico, de intervenção nutricional, envolvendo pacientes com AR. O diagnóstico de AR foi definido de acordo com os critérios do ACR de 1987 e/ou novos critérios classificatórios ACR/EULAR 2010 (MOTA et al., 2011).

O grupo de intervenção foi composto por 23 mulheres e instruídas a manter sua dieta habitual; e fazer ingestão de 500 mL de suco de cranberry de baixa caloria, da marca Juxx, por dia próximo ao almoço, sendo orientado também manter o suco em geladeira para uma melhor adesão. O grupo controle, composto por 18 mulheres. A composição de nutrientes de 500 ml de suco de cranberry é de: 50 kcal; 0 g de proteína; 12,5 g de carboidratos; 0 g de lipídeos, 0 g de fibra; 75 mg de sódio; 60 mg de vitamina C, 131.92 mg de proantocianidinas, 258,75 mg de fenólicos totais e 0,30 mg de ácido fólico. O poder antioxidante total do suco de cranberry é derterminado pela Capacidade Antioxidante Radical de Oxigênio (ORAC) foi de 183.65 µmol / mL.

Figura 4 - Composição nutricional do suco de cranberry normocalórico e de baixa caloria.

Cranberry

DADOS NUTRICIONAIS DATOS NUTRICIONALES		
Porção de 200ml (um copo) / Porción de 200ml (un vaso)		
Quantidade por porção / Cantidad por Porción		**%VD(*) %VD(*)**
Valor energético / Valor energetico 110kcal=460kJ		5
Carboidratos / Carbohidratos	26g	9
Proteínas / Proteínas	0g	0
Gorduras Totais / Grasas Totales	0g	0
Gorduras Saturadas / Grasas Saturadas	0g	0
Gorduras Trans / Grasas Trans	0g	**
Fibra Alimentar / Fibras Alimentícias	0g	0
Sódio / Sódio	30mg	1
Vitamina C / Vitamina C	60mg	130

Cranberry Zero

DADOS NUTRICIONAIS DATOS NUTRICIONALES		
Porção de 200ml (um copo) / Porción de 200ml (un vaso)		
Quantidade por porção / Cantidad por Porción		**%VD(*) %VD(*)**
Valor energético / Valor energetico 20kcal=84kJ		
Carboidratos / Carbohidratos	5g	
Proteínas / Proteínas	0g	0
Gorduras Totais / Grasas Totales	0g	0
Gorduras Saturadas / Grasas Saturadas	0g	0
Gorduras Trans / Grasas Trans	0g	
Fibra Alimentar / Fibras Alimentícias	0g	0
Sódio / Sódio	30mg	1
Vitamina C / Vitamina C	60mg	130

Fonte: Empresa Juxx

Critérios de inclusão e exclusão

Os critérios de inclusão dos pacientes com AR com diagnóstico confirmado e do sexo feminino, com idade entre 18 e 65 anos. Os critérios de exclusão foram a presença de doenças da tireóide, suprarrenais, renais, hepáticas, gastrointestinais, doenças infecciosas, oncológicas, outras doenças autoimunes, terapia de reposição hormonal e uso de suplementos antioxidantes.

Atividade da doença

Os pacientes foram classificados de acordo com os critérios de classificação do ACR/EULAR (ALETAHA et al., 2010), e o estado de atividade da doença foi determinada utilizando a DAS 28, conforme a equação descrita no site da DAS (“DAS28 - *Home of the Disease activity score* and DAS 28”, [s.d.]), por um único reumatologista. O DAS 28 considera a contagem de articulações inchadas e dolorosas, estado geral de saúde (EGS); avaliação do paciente da atividade da doença usando uma escala visual analógica de 100 mm em locais onde 0 = melhor, 100 = pior), além de níveis de sedimentação de eritrócitos (ESR) (mg/L).

Controle de adesão ao tratamento

Algumas medidas foram tomadas para aperfeiçoar e avaliar a adesão do

paciente. O suco de cranberry foi entregue no início da pesquisa. Após 90 dias, realizou-se a contagem das caixas de suco para verificar se a ingestão estava correta. O sabor marcante azedo com toque adocicado do suco foi a principal queixa relatada.

Além disso, foram realizadas entrevistas telefônicas para avaliar se os pacientes estavam usando corretamente o suplemento e para evitar mudanças no estilo de vida.

Aspectos éticos, consentimento, saúde e segurança

A pesquisa foi conduzida em conformidade com todas as normas estabelecidas de experimentação humana. Além disso, o Comitê de Ética em Pesquisa Envolvendo Seres Humanos da UEL aprovou todos os procedimentos envolvendo os participantes humanos, conforme aprovação de número CAAE: 13426014.6.0000.5231, Parecer CEP n. 617.289, de 14/04/2014 (Anexo 1) da UEL, e um termo de consentimento livre e esclarecido (TCLE) foi obtido de todos os indivíduos incluídos no estudo. Esta investigação clínica foi conduzida de acordo com os princípios expressos na Declaração de Helsinki e suas alterações posteriores. Todos os procedimentos obrigatórios de saúde e de segurança do laboratório foram cumpridos.

Dados demográficos, epidemiológicos, medidas antropométricas

As informações sobre o histórico médico foram obtidas na avaliação clínica realizada por médico reumatologista. Informações sobre a duração da doença, como também a utilização de medicamentos, anti-inflamatórios não-esteroides, corticosteróides, antimaláricos, contraceptivos orais, medicamentos anti-hipertensivos foram registradas para cada paciente, de acordo com o apêndice A. Os indivíduos de ambos os grupos relataram não fazer uso de bebidas alcoólicas regularmente.

As medidas antropométricas foram tomadas. O peso corporal foi medido com precisão de 0,1 kg no período da manhã, utilizando uma balança eletrônica, com os indivíduos vestindo roupas leves e sem sapatos; a altura foi medida com precisão de 0,1 cm usando um estadiômetro. O IMC foi calculado a partir do peso (kg) dividido pela altura (m) elevado ao quadrado. A circunferência abdominal (CA) foi

medida com os pacientes em pé, na metade da distância entre a face inferior da última costela e a porção superior da crista ilíaca e expressa em cm.

4.3 MARCADORES LABORATORIAIS

4.3.1 Análise Bioquímicas e Imunológicas

Após jejum de 12 horas, amostra de sangue venoso foi colhida usando tubos estéreis (BD Vacutainer® UltraTouch™, Franklin Lakes, NJ, EUA), sem anticoagulante ou contendo ácido etilenodiaminotetracético (EDTA). O sangue total foi deixado em repouso durante 30 minutos e centrifugado a 3000 força g durante 10 minutos. As amostras de plasma e de soro foram separadas e seguidamente distribuídas em alíquotas e armazenadas a -80°C para análises subsequentes.

Os níveis de colesterol total, lipoproteína de baixa e alta densidade, triacilglicerol e glicose foram avaliados por um auto-analisador bioquímico (Dimension Dade AR Dade Behring, Deerfield, IL, EUA) usando kits Dade Behring®. A análise de insulina foi realizada por imunoensaio enzimático de micropartículas (MEIA) utilizando o equipamento ABBOTT® AXSYM. A Avaliação do Modelo Homeostático (HOMA) é uma estimativa da resistência à insulina (IR) [20] e foi calculada pela seguinte fórmula: HOMA-IR = glicemia de jejum (mmol / L) x insulinemia de jejum (mU / L) /22,5.

As contagens de leucócitos, plaquetas e VHS foram determinados, respectivamente, pelos autoanalisadores hematológicos Mindray BC6800 e Alifax Test 1 THL. Os níveis de PCR no soro foram medidos usando um ensaio turbidimétrico (C8000, ABBOTT, Architect Abbot Laboratories, Abbott Park, IL, EUA). Os níveis séricos de ferritina foram determinados com um ensaio de micropartículas quimioluminescentes (Architect, Abbott Laboratory, Abbott Park, IL, EUA). Os títulos do FR foram medidos usando um ensaio turbidimétrico (C8000, ABBOTT, Architect Abbott Laboratories, Abbott Park, IL, EUA) e os resultados foram expressos como U / mL. Os anticorpos anti-CCP foram testados utilizando um imunoensaio de micropartículas quimioluminescentes (Architect, Abbott Laboratory, Abbott Park, IL, EUA) e os resultados foram expressos como U / mL. Os níveis plasmáticos totais de homocisteína foram medidos por quimioluminescência (ARCHITECT; Abbott Laboratory).

4.3.2 Análise Estatística

Os dados categóricos foram analisados com o teste do qui-quadrado ou exato de Fisher. Número absoluto e porcentagem demonstraram os resultados. O teste de pares casados de Wilcoxon foi realizado para verificar as alterações desde o início (alterações intragrupo). O teste de Mann-Withney foi realizado para comparar os valores basais e as diferenças entre os grupos de tratamento (alterações intergrupos). Os dados são expressos como medianas e percentis 25 a 75. Todas as análises estatísticas foram realizadas usando o IBM SPSS, versão do Windows 24. Os testes foram bicaudais e um nível alfa de 0,05 indicou resultados estatisticamente significativos. O tamanho da amostra foi estimado estatisticamente para cada grupo considerando um poder estatístico de 80% e o nível de significância bilateral de $p < 0,05$. O tamanho da amostra foi calculado para detectar diferenças estatísticas de pelo menos 10% nos parâmetros avaliados. O programa Cal Stat foi utilizado para o cálculo do tamanho da amostra, com base na média e no desvio padrão para alguns dos parâmetros avaliados anteriormente em outros estudos.

5 RESULTADOS

Artigos científicos

O presente estudo deu origem a dois trabalhos: o primeiro, um artigo de revisão intitulado "The impact of Cranberry (Vaccinium macrocarpon) and cranberry products on each component of the Metabolic Syndrome: a review", publicado na revista da Sociedade Brasileira de Alimentação e Nutrição Nutrire 42:25; 2017. O segundo, um artigo científico original intitulado "Cranberry Juice Decreases Disease Activity in Patients with Rheumatoid Arthritis", encaminhado para a revista Nutrition: The international journal of applied and basic nutritional sciences, com fator de impacto 3.420.

5.1 ARTIGO 1:

The impact of Cranberry (*Vaccinium macrocarpon*) and cranberry products on each component of the Metabolic Syndrome: a review

Nataly Simões Bandiera Thimóteo[1], Bruna Miglioranza Scavuzzi[2], Andréa Name Colado Simão[3], Isaias Dichi[4*]
[1] Post Graduate Program in Health Science – University of Londrina. Rua Robert Koch no 60 Bairro Cervejaria. Londrina, Paraná, Brazil. Email: naty_bandiera@hotmail.com
[2] Post Graduate Program in Health Science – University of Londrina. Rua Robert Koch no 60 Bairro Cervejaria. Londrina, Paraná, Brazil. Email: b_miglioranza@yahoo.com.br
[3] Department of Pathology, Clinical Analysis and Toxicology – University of Londrina. Rodovia Celso Garcia Cid - PR 445, Km 380 – Londrina, Paraná, Brazil. Email: deianame@yahoo.com.br
[4] Department of Internal Medicine – University of Londrina. Rua Robert Koch no 60 Bairro Cervejaria. Londrina, Paraná, Brazil. Email: dichi@sercomtel.com.br

*Corresponding author: Isaias Dichi, MD, PhD.
Postal address: Department of Internal Medicine. Rua Robert Koch nº 60 Bairro Cervejaria. Universidade Estadual de Londrina. Londrina, Paraná, Brazil. Zip-code: 86038-440. Telephone: +55-43-3371-2234; Fax: +55-43-3371-2619.
E-mail address: dichi@sercomtel.com.br

ABSTRACT

Some studies have shown that cranberry (*Vaccinium macrocarpon*) has beneficial effects on the components of the Metabolic Syndrome (MetS), a condition characterized by a cluster of cardiovascular risk factors such as central obesity, hypertension, impaired glucose homeostasis, elevated triglycerides and decreased high density lipoprotein (HDL) cholesterol levels. Cranberry is very rich in polyphenols, which may significantly reduce cardiovascular disease (CVD) risk. Nutritional intervention studies have indicated that the intake of

cranberries and cranberry products may have the following impact on metabolic health: 1) to attenuate markers of obesity such as body weight, body mass index (BMI) and waist circumference (WC). 2) to reduce systolic and diastolic pressures. 3) to decrease plasma concentrations of triglycerides and oxidized low density lipoprotein LDL-cholesterol, as well as increase HDL cholesterol. 4) to promote glucose homeostasis. In addition, nutritional intervention with cranberries could confer antioxidant and anti-inflammatory properties, and the ability to reduce biomarkers of atherosclerosis associated with the MetS, such as homocysteine. Although there has been promising results, particularly related to lipid profile and blood pressure, further research is needed to support the recommendation of cranberry intake as a nutritional intervention for the treatment of MetS.

Keywords: cranberry, inflammation, bioactive compounds, polyphenols, metabolic syndrome.

BACKGROUND

Metabolic Syndrome (MetS) is generally defined as a complex disorder represented by a cluster of cardiovascular risk factors such as central obesity, dyslipidemia, hypertension and impaired glucose metabolism, leading to an increased risk of coronary heart diseases, other types of atherosclerotic cardiovascular diseases and type 2 diabetes (DT2) [1]. *Recent evidence suggests* that the prevalence of MetS is increasing in both developed and developing countries, such as Brazil [2,3].

Diets rich in fruits and vegetables, especially those considered berries, increase the intake of polyphenols, which are known to confer *benefits* to the *cardiovascular* health [4,5]. Cranberries (*Vaccinium macrocarpon*) are *native fruits* from *North America* that contain low carbohydrate concentrations in comparison to other fruits. Furthermore, they have high content of vitamins, minerals and polyphenolic compounds [6], such as flavan-3-ols, anthocyanins, benzoic acid and ursolic acid [7]. A-*type proanthocyanidins* are also present in high concentrations in cranberry, while other berries predominantly have B-*type proanthocyanidins. B-type proanthocyanidins are believed to be* less bioavailable than the A-type [8]. The most abundant flavonoids in cranberries consist mainly of quercetin and myricitrin [7].

Moreover, it has been demonstrated that cranberry juice may contain resveratrol in concentrations similar to grape juice [9]. Resveratrol has several biological effects related to cardiovascular health, including inhibition of platelet aggregation and reduction of inflammation [6]. The polyphenols present in cranberry have a wide variety of biological effects, including antibacterial, anticarcinogenic, antiangiogenic, anti-inflammatory, antioxidant, modulating enzyme activity and gene expression regulation [7,10–16].

In addition to polyphenolic compounds, cranberry is rich in vitamins and minerals. Cranberry juice, for example, may contain 100% of the daily requirement of vitamin C, contributing to the beneficial effects of the fruit [10]. Cranberries can be consumed in various products such as industrialized juice, jam, frozen fruit pulp, sauce, cereal bars and capsules and have become increasingly popular and consumed, after several researches have indicated *health benefits* including possibly *preventing diseases* such as urinary tract infection [17].

According to observational and interventional studies in humans, consumption of cranberry and cranberry products may be associated with beneficial effects on MetS, affecting one or more of its components [6,18], a variety of inflammatory biomarkers and oxidative stress [19]. Thus, the present review gathers recent and relevant literature involving the consumption of cranberry products and the components of the MetS in humans, in addition to highlighting the most relevant mechanisms involved.

CRANBERRY AND OBESITY

Obesity has become a major public health issue and it is growing worldwide. In 2012, approximately 34.9% of American adults were classified as obese [20]. Obesity is usually defined when body mass index (BMI) is greater than or equal to 30 kg/m^2. Abdominal *obesity* is defined as a waist *circumference (WC)* above *102 cm* in *men* and *88 cm* in *women* [21].

Studies have demonstrated that bioactive compounds such as flavonoids have the potential to inhibit lipogenesis and adipogenesis, stimulate lipolysis and to induce apoptosis in adipocytes [22]. Diet is closely related to the development of obesity, therefore a diet enriched with these compounds may serve as an additional strategy for the prevention and treatment of obesity. It has been previously demonstrated that cranberry reduces the proliferation and viability of 3T3-L1 pre-adipocytes in a dose-dependent manner. A nutritional intervention with this berry also reduced the number of adipocytes and reduced the accumulation of lipids in the 3T3-L1 pre-adipocytes, demonstrating an inhibitory effect on lipogenesis. Furthermore, it was observed that cranberry induced lipolysis in adipocytes and reduced the expression of the main transcription factors of the adipogenesis pathway, such as PPARγ, C/EBPb e SREBP1 [23].

The main *human-interventional* studies with cranberry or cranberry products considering markers of obesity are listed in Table 1.

Table 1. Intervention studies with cranberry products evaluating markers of obesity

Authors	Studies	Population / intervention	Conclusion
Ruel et al., 2006 [24]	Intervention study to evaluate the effect of increasing daily consumption of a low-calorie cranberry juice cocktail on plasma lipid profile in abdominally obese men.	30 men consumed increasing doses of cranberry juice for three consecutive 4-week periods (125 mL, 250 mL e 500 mL/d).	There was a decrease in adiposity measures after the intervention period, with reduction of body weight ($p = 0.0263$), BMI ($p = 0.0386$) and WC ($p < 0.0001$).
Basu et al., 2011 [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice / day (n = 15) or placebo (n = 16) for 8 weeks.	Consumption of 480 mL of cranberry juice /day for 8 weeks showed no significant effect on WC reduction.
Duffey and Sutherland, 2013 [25]	A study to verify the association between consumption of cranberry beverage, macronutrient intake and body mass of patients who participated in the National Health and Nutrition Examination Survey (NHANES) between 2005-2008.	10891 American adults aged 19 years or older selected by the National Health and Nutrition Examination Survey (NHANES) between 2005-2008.	Consumers of cranberry drinks were more likely to have normal body weight ($p < 0.001$) and less likely to be overweight or obese (BMI ≥ 25 kg/m^2, $p < 0.001$) compared to non-consumers.
Simão et al., 2013 [6]	Clinical trial to evaluate the effect of intake of low calorie cranberry juice on metabolic and inflammatory biomarkers in MetS patients.	56 patients with MetS participated in a 60-day study; 20 patients consumed 700 mL of cranberry juice / day and 36 did not consume the juice.	The consumption of 700 mL of cranberry juice / day for 60 days showed no significant effects on the reduction of BMI or WC.

BMI, body mass index; CVD, cardiovascular disease; WC, waist circumference; MetS, metabolic syndrome.

Thus, there are still very few clinical and epidemiological studies evaluating the relationship between cranberry consumption and body composition. Therefore, more work is needed to obtain stronger evidence.

CRANBERRY AND GLUCOSE METABOLISM

Glucose homeostasis is disturbed when insulin and fasting glucose are greater than 20 mU / mL and 110 mg / dL, respectively, or when the patient has to use medication to control blood glucose [26]. Matthews et al., 1985, described a mathematical relationship (HOMA-IR model) between fasting glycemia and insulin to predict insulin resistance [27]. Lower HOMA-IR values represent higher insulin sensitivity and higher values correspond to decreased insulin sensitivity, also known as insulin resistance (IR). IR and hyperinsulinemia contribute to the pathogenesis of type 2 diabetes [28].

Wilson et al., 2010 studied postprandial insulin and glucose response in patients with type 2 diabetes. The subjects were allocated into four groups that received: a single serving of white bread (57 g, 160 calories, 1 g of fiber); raw cranberries (55 g, 21 calories, 1 g of fiber); sweetened cranberries (40 g, 138 calories, 2.1g fiber); or cranberries with low sugar and high fiber content (40 g, 113 calories, 1.8 g of fiber and 10 g polydextrose [29]. The investigators found that the consumption of low-sugar, high-fiber cranberries resulted in more favorable glucose and insulin peaks. Thus, the selection of dry cranberries, a natural source of polyphenols and fibers, would enable a more favorable glycemic response in patients with T2D. The decrease in glucose peak may be due to the presence of the soluble fibers polydextrose and β-Glucan, which were present in the low-calorie serving, since these compounds have been related to the reduction in the rate of gastric glucose absorption [30,31]. The presence of flavonoids in cranberry juice can also delay the intestinal absorption of glucose [32], contributing to the improvement in the glycemic response observed in previous studies carried out by the same research group [33].

In vitro studies have demonstrated that the extent of inhibition of α-glucosidase by berry extracts is related to its anthocyanin content [34]. Cyanidin-3-rutinoside [35] and cyanidin-3-galactoside [36] are considered α-glucosidase inhibitors. Proanthocyanidins are also considered potent α-glucosidase inhibitors [37]. Barrett et al., 2013 conducted an *in vitro* study to investigate if the tannins (proanthocyanidins and elagitannins) present in pomegranate, cranberry, grape and cocoa extracts could bind to the digestive enzymes α-amylase and glucoamylase, thus inhibiting starch hydrolysis. The authors concluded that not only were tannins capable of inhibiting these enzymes, but also that larger and more complex tannins such as cranberries would have the ability to inhibit enzymes more effectively than less polymerized tannins, such as those present in cocoa [38]. Another *in vitro* study has shown that cranberry procyanidins have the ability to inhibit the glycation of human hemoglobin and serum albumin by elimination of reactive carbonyl radicals [39].

Some phenolic acids, such as chlorogenic, ferulic and caffeic acids, competitively inhibit glucose uptake mediated by *sodium*-dependent *glucose transporter 1* (*SGLT1*) [19].

This inhibition has also been observed by other glucosides and quercetin [32]. *SGLT1* assists in the intestinal absorption of glucose through the aid of sodium-dependent transport, and thereby facilitates the independent transport of sodium via GLUT (9). The flavonoids mycetin and quercetin were responsible for the inhibition of GLUT2 glucose transport (37-38). These compounds that *inhibit glucose uptake*, such as phenolic acids and flavonoids, are components present in berries [41–43]. Furthermore, it has been demonstrated in porcine models that quercetin inhibits gastric uptake of glucose. Quercetin and myricetin have also been shown to inhibit GLUT4-mediated glucose uptake in rodent adipocytes, to inhibit aldose reductase, α-amylase and α-glucosidase *in vitro* [44].

Although polyphenolic compounds present in berries have been associated with the enhancement of *glycemic* regulation, *other components* may contribute to these effects. Törrönen et al, 2013 investigated the effects of whole-berry *purées* on the postprandial glucose and insulin responses after consumption of white wheat bread or rye bread. The berry mixture (strawberries, bilberries, cranberries, and blackcurrants) significantly reduced the postprandial insulin response after the intake of white wheat bread or rye bread. The researchers observed that although the consumption of berries did not suppress postprandial peak glucose, less insulin was required for the maintenance of postprandial glucose metabolism [45]. According to the investigators, the more desirable postprandial insulin response did not appear to be related to the polyphenol composition of the berries, but rather the fiber content, especially soluble fiber [45].

The main *human-interventional* studies with cranberry or cranberry products considering glycemic metabolism are listed in Table 2.

Table 2. Intervention studies with cranberry products evaluating markers of glucose metabolism

Authors	Studies	Population / intervention	Conclusion
Lee et al., 2008 [46]	A randomized double blind, controlled study evaluating the effect of cranberry intake on the lipid profile of patients with T2D.	30 type 2 diabetic subjects received cranberry supplements (500 mg/capsule) or placebo, 3x/day, for 12 weeks.	Neither fasting glucose nor glycated hemoglobin improved in either group.
Basu et al., 2011 [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice / day (n = 15) or placebo (n = 16) for 8 weeks.	Consumption of 480 mL of cranberry juice per day for 8 weeks showed no significant effect on the reduction of fasting glycemia.
Shidfar et al., 2012 [44]	A randomized, double-blind, placebo-controlled clinical trial to verify the effect of cranberry juice on PON-1, apoA-1, apoB, glucose and Lp (a) in T2D patients.	Patients with T2D consumed 240 mL of juice / day (n = 29) or placebo (n = 29) for 12 weeks.	Patients who consumed cranberry juice had a significant decrease in serum glycemia when compared to the initial value (P <0.01) and the control group (P <0.05).
Novotny et al, 2015 [47]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of juice (n = 29) or placebo (n = 27) two times/day for 8 weeks.	Patients who consumed low-calorie cranberry juice had a reduction in fasting plasma glucose (P = 0.03). The juice also had a beneficial effect on HOMA-IR for participants with high baseline values (P = 0.035).

MetS, metabolic syndrome; PON-1, paraoxonase-1; Lp (a), lipoprotein (a); T2D, type two diabetes mellitus.

CRANBERRY AND BLOOD PRESSURE

Polyphenols may significantly reduce cardiovascular disease (CVD) risk [48,49]. In a study conducted during 18 years, it was demonstrated that the combined intake three times a week of blueberries and strawberries (two anthocyanin-rich foods) was associated with a lower risk of myocardial infarction in middle-aged women [5]. Cranberries are rich sources of several polyphenols, such as quercetin which has been associated with significant blood pressure reduction in animal models [50–53] and human trials [50–53]. Thirty men participated in a 12-week intervention study and were asked to consume increasing daily doses of a cranberry juice cocktail (125, 250 and 500 mL/day) over three successive periods of 4 weeks. The investigators noted a slight but significant decrease in SBP (-3 mm Hg) over

the course of the intervention [54]. This reduction was likely associated with the polyphenolic content of the beverage.

Furthermore, nutritional studies have associated the intake of berries, tea, soy and cocoa products - all with high polyphenol contents - with cardioprotective effect [48,55–57]. Blueberries are known for their significant amount of fibers and micronutrients [58–60]. Intervention studies with blueberries, flavonoids and anthocyanins have indicated that possible mechanisms for the reduction of blood pressure are inhibition of the activity of the angiotensin-converting enzyme [54], a significant increase in nitric oxide synthesis by endothelial cells [61,62], reduction of vasoconstriction via nitric oxide-mediated pathway or reduction of renal oxidative stress [63,64]**.** Dietary intervention with polyphenol-rich foods and berry beverages has led to significant changes in MetS characteristics, including reduction of blood pressure, abdominal adiposity, dyslipidemia, inflammation and oxidative stress [65]**.**

The main *human-interventional* studies with cranberry or cranberry products considering blood pressure are listed in Table 3.

Table 3. Intervention studies with cranberry products evaluating blood pressure

Authors	Studies	Population / intervention	Conclusion
Ruel et al., 2008 [54]	Intervention study to determine the effect of the daily consumption of low-calorie cranberry juice cocktail on plasma oxidized LDL, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin concentrations in men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125 mL, 250 mL e 500 mL/d).	There was a slight but significant decrease in systolic blood pressure over the course of the intervention (-3 mm Hg, P= 0.03).
Basu et al., 2011 [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice / day (n = 15) or placebo (n = 16) for 8 weeks.	Consumption of 480 mL of cranberry juice per day for 8 weeks showed a non-significant reduction in systolic blood pressure compared to baseline values (-5.3%, P = 0.07).
Novotny et al, 2015 [66]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of cranberry juice (n = 29) or placebo (n = 27) two times/day for 8 weeks.	After 8 weeks, diastolic pressure was significantly lower in the cranberry juice group than in the placebo group (P = 0.048), with no difference in systolic pressure.

CVD, cardiovascular disease; MetS, metabolic syndrome.

CRANBERRY AND DYSLIPIDEMIA

Cardiovascular diseases are among the leading causes of death in North America [67,68]. Although LDL cholesterol is not included in the definition of metabolic syndrome, elevated concentration of low-density lipoprotein (LDL) is one of the most important cardiovascular risk factor [69]. LDL particles, such as oxidized LDL, could at least partially explain the *atherogenicity of LDL* [70,71]. Oxidized LDL is not recognized by LDL receptors, but rather by cell-*surface receptors* on *macrophages*; oxidation of LDL promotes cholesterol absorption, leading to the formation of foam cells, which is the first step in the formation of the first atherosclerotic lesions (67). A decrease in HDL concentration is also an independent risk factor for CVD [72]. *Although the role of HDL* in the *cholesterol transport* is known, HDL has several other cardioprotective effects such as antithrombogenic, antioxidant, fibrinolytic, antiadherence and anti-inflammatory properties [73].

The lipid-lowering effects of cranberry can be attributed mainly to the phytochemical compounds contained in the fruit and to the fiber content, depending on the form of consumption. Cranberry is a relevant source of flavonoids, such as anthocyanidins, proanthocyanidins [74,75], resveratrol [76] and phenolic acid [74]. Flavonoids, abundantly present in cranberry, would have the ability to inhibit the oxidation of LDL-cholesterol (1). Oxidized LDL plays a critical role in the initiation and progression of atherosclerosis, thus, supplementation with cranberry would have the potential to delay the process of atherosclerotic CVD [77]. In addition, flavonoids would have the ability to inhibit platelet adhesion and aggregation, inhibit enzymes involved in lipid and lipoprotein metabolism and could increase reverse cholesterol transport, lowering total and LDL cholesterol [78].

Anthocyanin-rich products reduced triglycerides in animal models [79–81] and inflammatory factors in humans [82,83]. Furthermore, several studies have shown that antioxidant compounds, especially polyphenols, can inhibit the oxidation of LDL, which in turn, would reduce the expression of adhesion molecules in the endothelium [84,85]. In addition, cranberry has salicylic acid [86], which has anti-inflammatory activity and has been shown to decrease the expression of vascular cell-1 adhesion molecule in vitro [87].

In addition, the total dietary fiber content of cranberry may reach 5 g / 100 g in dried fruit and thus may contribute to its cholesterol lowering effects (4). The main *human-interventional* studies with cranberry or cranberry products considering lipid profile are listed in Table 4.

Table 4. Intervention studies with cranberry products evaluating lipid profile

Authors	Studies	Population / intervention	Conclusion
Ruel et al., 2005 [88]	Intervention study to evaluate the impact of cranberry juice consumption on LDL oxidation and on the antioxidant capacity of plasma.	21 healthy men, consuming cranberry juice (7 mL / kg body weight / day) for 14 days.	After 14 days, no change was observed in the levels of LDL-HDL and oxidized LDL.
Ruel et al., 2006 [12]	Intervention study to evaluate the effect of increasing daily consumption of a low-calorie cranberry juice cocktail on plasma lipid profile in abdominally obese men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125 mL, 250 mL e 500 mL/d).	After 12 weeks, there was a significant increase in HDL ($p = 0.001$), reduction in TGs ($p = 0.0553$), and significant decrease in total cholesterol / HDL ratio ($p = 0.0005$).
Ruel, et al., 2007 [13]	Controlled intervention study evaluating the effect of low-calorie cranberry juice on plasma oxidized LDL, ICAM-1 and VCAM-1 in healthy subjects.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125 mL, 250 mL e 500 mL/d).	The intervention produced a decrease in the plasma concentration of oxidized LDL ($p <0.0001$), a significant increase in plasma HDL-cholesterol ($p = 0.0010$), but did not significantly affect TG concentration, total cholesterol levels and LDL cholesterol.
Lee et al., 2008 [46]	A randomized double blind, controlled study evaluating the effect of cranberry intake on lipid profile in patients with T2D.	30 type 2 diabetic subjects received cranberry supplements (500 mg/capsule) or placebo, 3x/day, for 12 weeks.	Supplementation with cranberry is effective in reducing the arteriosclerotic cholesterol profile, including LDL, total cholesterol, and total cholesterol / HDL ratio.
Basu et al., 2011 [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice / day ($n = 15$) or placebo ($n = 16$) for 8 weeks.	The consumption of 480 mL of cranberry juice / day for eight weeks did not show significant effects on reduction of lipid profile.
Novotny et al., 2015 [66]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of cranberry juice ($n = 29$) or placebo ($n = 27$) two times/day for 8 weeks.	TGs were lower for those who consumed cranberry juice compared to the placebo group ($p = 0.027$). No differences in serum total cholesterol, LDL, and HDL.

ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; TGs, triglycerides.

CRANBERRY AND MARKERS OF INFLAMMATION AND OXIDATIVE STRESS

Central obesity and insulin resistance are the main features involved in MetS, but low-grade chronic inflammation is considered a major link between the MetS and CVD [89]. In MetS, central obesity is considered an important source of low grade chronic inflammation [90].

Free radicals and reactive metabolites, also known as reactive oxygen species (ROS), are normal products of cellular metabolism and are generated primarily by the mitochondrial respiratory chain. When there is an imbalance between the production of these reactive species and their elimination by antioxidant mechanisms, an accumulation of ROS occurs, leading to oxidative stress. Several diseases such as cancer, chronic inflammatory diseases and aging are all conditions associated with increased oxidative stress [91–94]. Furthermore, continuous oxidative stress may lead to chronic inflammation [95].

In a comparative study, cranberry juice had the same amount of resveratrol as grape juice [76]. The health benefits associated to resveratrol are many, especially in promoting cardiovascular health, elimination of reactive oxygen species, inhibition of platelet aggregation, and decrease of inflammation [96].

Although cranberries are rich in known antioxidant substances, the number of *human-interventional* studies with this berry considering oxidative stress is unexpectedly scarce. The main intervention studies considering oxidative stress and markers of inflammation are shown in Table 5.

Table 5. Intervention studies with cranberry products evaluating markers of inflammation and oxidative stress.

Authors	Studies	Population / intervention	Conclusion
Ruel et al., 2006 [24]	Intervention study to evaluate the effect of increasing daily consumption of a low-calorie cranberry juice cocktail on plasma lipid profile in abdominally obese men.	30 men consumed increasing doses of cranberry juice for 3 consecutive 4-week periods (125 mL, 250 mL e 500 mL/d).	Reduction of nitrite / nitrate concentration (P <0.05) with a significant association between plasma nitrite / nitrate decrease and apo A-1 increase (P <0.05). After the 12-week period, the antioxidant capacity of total plasma increased significantly (p = 0.006).
Basu et al., 2011 [16]	Randomized, double-blind, placebo-controlled clinical trial to assess the effect of intake of low calorie cranberry juice on CVD risk factors such as lipid oxidation, inflammation, and dyslipidemia in subjects with MetS.	31 patients with MetS consumed 480 mL of juice / day (n = 15) or placebo (n = 16) for 8 weeks.	Cranberry juice significantly increased plasma antioxidant capacity (P<0.05) and decreased oxidized LDL and malondialdehyde (P<0.05) at 8 weeks versus placebo.
Simão et al., 2013 [6]	Clinical trial to evaluate the effect of low calorie cranberry juice intake on metabolic and inflammatory biomarkers in MetS patients.	56 patients with MetS participated in a 60-day study; 20 patients consumed 700 mL of cranberry juice / day and 36 did not consume the juice.	The consumption of 700 mL of cranberry juice / day for 60 days decreased lipoperoxidation (P=0.036) and protein oxidation (P=0.008) and increased adiponectin levels (p = 0.01). The metabolic and inflammatory biomarkers C-reactive protein, TNF-α, IL-1 and IL-6 did not differ between the groups.
Novotny et al., 2015 [66]	A double blind, placebo-controlled study evaluating the consumption of low-calorie cranberry juice and placebo drink to decrease cardiometabolic risk in overweight middle-aged population.	Overweight patients consumed 240 mL of cranberry juice (n = 29) or placebo (n = 27) two times/day for 8 weeks.	After eight weeks of evaluation, there was no improvement in C-reactive protein levels (p = 0.967).

CVD, cardiovascular disease; MetS, metabolic syndrome; TNF, Tumor Necrosis Factor; IL, Interleukin.

CRANBERRY AND OTHER MARKERS OF CARDIOVASCULAR RISK

The intake of fruits and vegetables is beneficial for reducing the risks of some human diseases, such as CVD and cancer. In addition to being rich in soluble and insoluble fibers,

the positive health effects are attributed to elements with antioxidant properties such as vitamins E, C and carotenoids, which have the capacity to inactivate ROS involved in the process or progression of chronic diseases [97]. The presence of anthocyanins in berries is *responsible* for *its coloration*, and comprises the largest group of natural species with water soluble vegetable pigments [98–101]. Normally, the intensity of the color is directly proportional to its anthocyanin content, and can range from 2-4 g / kg, increasing as berries ripen. The average anthocyanin consumption in the United States of America is 12.5-215 mg per day [102]. *Studies have shown* that *anthocyanins have low bioavailability*, are widely conjugated in the liver and the intestine, *and excreted* by the kidney *within 2-8* h of ingestion [103,104]. The content of polyphenols (including anthocyanins) and some vitamins in berries may be affected by post-harvest processing techniques, such as pressing and *pasteurization*, and thus reduce their effects on CVD risk [105–107].

In an *in vitro* study, anthocyanins were shown to be effective biomarkers of heart diseases and cancer, inhibiting the release of ROS from active human granulocytes [108], and suppressing free radical-mediated lipid peroxidation and apoptosis in cultured aortic endothelial cells [109,110]. In addition, anthocyanins, aglycones and glycosides are effective inhibitors of oxidative-induced DNA damage in human colon cells [111] and are potent inhibitors of tumor cell growth in vitro [112,113].

Table 6. Studies considering cardiovascular risk markers and consumption of cranberry

Authors	Studies	Population / intervention	Conclusion
Dohadwala et al, 2011 [15]	This study was carried out in two stages: 1) an uncontrolled pilot study to determine the acute effects of cranberry juice consumption; 2) randomized, double blind, cross-over study to examine vascular functions before and after consumption of cranberry juice and placebo in patients with stable coronary disease.	An acute non-placebo pilot study in participants (n=15) who consumed 480 mL cranberry juice and a placebo crossover study (n = 44) 480 mL / day for 4 weeks with 2-week washout period between placebo / cranberry drinks.	After the pilot study, there was a significant improvement in the brachial artery dilation. No effects on blood pressure, basal or hyperemic flow were observed. In the crossover study, there was a significant decrease of arterial stiffness with consumption of the cranberry beverage.
Simão et al., 2013 [6]	Clinical trial to evaluate the effect of intake of low calorie cranberry juice on metabolic and inflammatory biomarkers in MetS patients.	56 patients with MetS participated in a 60-day study; 20 patients consumed 700 mL of cranberry juice / day and 36 did not consume the juice.	The consumption of 700 mL of cranberry juice / day for 60 days significantly decreased homocysteine levels (p<0,001).

MetS, metabolic syndrome.

CONCLUSION

Although several studies have shown beneficial effects, there are still few clinical and epidemiological studies evaluating the relationship between cranberry intake and the various components directly or indirectly associated with the MetS. In addition, most clinical studies are of relatively short duration (8 to 12 weeks), which often prevents the verification of additional beneficial effects. Another factor to consider is the amount of product to be ingested. The antioxidant action of cranberry is already well known and some authors have suggested the conduction of clinical trials to verify anti-inflammatory activity. The mechanisms of action associated to cranberry also require further studies. Although results especially related to lipid profile and blood pressure are promising, further research is needed to support the recommendation of cranberry intake as a nutritional intervention for the treatment of metabolic syndrome.

LIST OF ABBREVIATIONS

BMI: Body mass index
BP: Blood pressure
CRP: C-reactive protein
CVD: cardiovascular disease;
FFAs: Free fatty acids
HDL: High-density lipoprotein
HOMA: Homeostatic model assessment
ICAM-1: intercellular adhesion molecule-1
IL: Interleukin
IR: Insulin resistance
LDL: Low-density lipoprotein
MetS: Metabolic syndrome.
Ox-LDL: Oxidized LDL
PAI-1: Plasminogen activator inhibitor-1
ROS: Reactive Oxygen Species
SBP: Systolic blood pressure
T2D: type 2 diabetes
TG: Triglycerides
VCAM-1: vascular cell adhesion molecule-1
WC: waist *circumference*

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

NSBT, BMS and ID performed the bibliographic research and writing. ANCS and ID conceived, designed, and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

REFERENCES

1. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. Nutrition. 1997;13:65; discussion 64, 66.
2. Ford E, Giles W, Mokdad A. Increasing prevalence of the metabolic syndrome among u.s. Adults. Diabetes Care. 2004;27:2444–9.
3. Grundy S. Metabolic syndrome pandemic. Arter Thromb Vasc Biol. 2008;28:629–36.
4. Reed J. Cranberry flavonoids, atherosclerosis and cardiovascular health. Crit Rev Food Sci Nutr. 2002;42:301–16.
5. Cassidy A, Mukamal KJ, Liu L, Franz M, Eliassen AH, Rimm EB. High Anthocyanin Intake Is Associated With a Reduced Risk of Myocardial Infarction in Young and Middle-Aged Women. Circulation. 2013;127:188–96.

6. Simão TNC, Lozovoy MAB, Simão ANC, Oliveira SR, Venturini D, Morimoto HK, et al. Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome. Br J Nutr. 2013;110:1885–94.
7. Blumberg JB, Camesano TA, Cassidy A, Kris-etherton P, Howell A, Manach C, et al. Cranberries and Their Bioactive Constituents in Human Health. Adv Nutr. 2013;4:618–32.
8. Appeldoorn MM, Vincken JP, Aura AM, Hollman PCH, Gruppen H. Procyanidin dimers are metabolized by human microbiota with 2-(3,4-dihydroxyphenyl)acetic acid and 5-(3,4-dihydroxyphenyl)-gamma-valerolactone as the major metabolites. J Agric Food Chem. 2009;57:1084–92.
9. Ruel G, Couillard C. Evidences of the cardioprotective potential of fruits: the case of cranberries. Mol Nutr Food Res. 2007 Jun;51:692–701.
10. McKay DL, Blumberg JB. Cranberries (Vaccinium macrocarpon) and cardiovascular disease risk factors. Nutr Rev. 2007 Nov;65:490–502.
11. Kim MJ, Jung HN, Kim KN, Kwak H-K. Effects of cranberry powder on serum lipid profiles and biomarkers of oxidative stress in rats fed an atherogenic diet. Nutr Res Pract. 2008;2:158–64.
12. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Favourable impact of low-calorie cranberry juice consumption on plasma HDL-cholesterol concentrations in men. Br J Nutr. 2006;96:357–64.
13. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men. Br J Nutr. 2008;99:352–9.
14. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily Cranberry Juice for the Prevention of Asymptomatic Bacteriuria in Pregnancy: A Randomized, Controlled Pilot Study. J Urol. 2008;180:1367–72.
15. Dohadwala MM, Holbrook M, Hamburg NM, Shenouda SM, Chung WB, Titas M, et al. Effects of cranberry juice consumption on vascular function in patients with coronary artery disease 1 – 3. Am J Clin Nutr. 2011;934–40.
16. Basu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. Nutr Res. 2011 Mar;31:190–6.
17. Franco L. Cranberry terapêutica. Globo News. 2010;
18. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Plasma matrix metalloproteinase (MMP)-9 levels are reduced following low-calorie cranberry juice supplementation in men. J Am Coll Nutr. 2009;28:694–701.

19. Blumberg JB, Basu A, Krueger CG, Lila MA, Neto CC, Novotny JA, et al. Impact of Cranberries on Gut Microbiota and Cardiometabolic Health: Proceedings of the Cranberry Health Research Conference 2015. Adv Nutr An Int Rev J. 2016;7:759S – 770S.
20. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. Jama. 2014;311:806–14.
21. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995;311:158–61.
22. Kowalska K. Naturalne związki zaangażowane w kontrolę masy tkanki tłuszczowej w badaniach in vitro * Natural compounds involved in adipose tissue mass control in in vitro studies. Postep Hig Med Dosw. 2011;65:515–23.
23. Kowalska K, Olejnik A, Rychlik J, Grajek W. Cranberries (Oxycoccus quadripetalus) inhibit adipogenesis and lipogenesis in 3T3-L1 cells. Food Chem. 2014;148:246–52.
24. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Favourable impact of low-calorie cranberry juice consumption on plasma HDL-cholesterol concentrations in men. Br J Nutr. 2006;96:357–64.
25. Duffey KJ, Sutherland LA. Adult cranberry beverage consumers have healthier macronutrient intakes and measures of body composition compared to non-consumers: National health and nutrition examination survey (NHANES) 2005-2008. Nutrients. 2013;5:4938–49.
26. National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetol. 1985;28:412–9.
28. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37:1595–607.
29. Wilson T, Luebke J, Morcomb E, Carrell E, Leveranz M, Kobs L, et al. Glycemic responses to sweetened dried and raw cranberries in humans with type 2 diabetes. J Food Sci. 2010;75:H218–23.
30. Xavier F. The role of viscous soluble fiber in the metabolic control of diabetes. Diabetes Care. 1997;20:1774.
31. Casiraghi MC, Garsetti M, Testolin G, Brighenti F. Post-prandial responses to cereal products enriched with barley beta-glucan. J Am Coll Nutr. 2006;25:313–20.

32. Cermak R, Landgraf S, Wolffram S. Quercetin glucosides inhibit glucose uptake into brush-border-membrane vesicles of porcine jejunum. Br J Nutr. 2004;91:849–55.
33. Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N. Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. J Food Sci. 2008;73:H241–5.
34. McDougall GJ, Shpiro F, Dobson P, Smith P, Blake A, Stewart D. Different polyphenolic components of soft fruits inhibit alpha-amylase and alpha-glucosidase. J Agric Food Chem. 2005;53:2760–6.
35. Adisakwattan S, Ngamrojanavanich N, Kalampakorn K, Tiravanit W, Roengsumran S, Yibchok-Anun S. Inhibitory activity of cyanidin-3-rutinoside on alpha-glucosidase. Enzyme. 2004;19:313–6.
36. Adisakwattana S, Charoenlertkul P, Yibchok-Anun S. α-Glucosidase inhibitory activity of cyanidin-3-galactoside and synergistic effect with acarbose. J Enzym Inhib Med Chem. 2009;24:65–9.
37. Schäfer A, Högger P. Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol) effectively inhibit α-glucosidase. Diabetes Res Clin Pract. 2007;77:41–6.
38. Barrett A, Ndou T, Hughey CA, Straut C, Howell A, Dai Z, et al. Inhibition of α-amylase and glucoamylase by tannins extracted from cocoa, pomegranates, cranberries, and grapes. J Agric Food Chem. 2013;61:1477–86.
39. Liu H, Liu H, Wang W, Khoo C, Taylor J, Gu L. Cranberry phytochemicals inhibit glycation of human hemoglobin and serum albumin by scavenging reactive carbonyls. Food Funct. 2011;2:475–82.
40. Johnston K, Sharp P, Clifford M, Morgan L. Dietary polyphenols decrease glucose uptake by human intestinal Caco-2 cells. FEBS Lett. 2005;579:1653–7.
41. Määttä-Riihinen KR, Kamal-Eldin A, Mattila PH, Gonzalez-Paramas AM, Törrönen R. Distribution and contents of phenolic compounds in eighteen scandinavian berry species. J Agric Food Chem. 2004;52:4477–86.
42. Määttä-Riihinen KR, Kamal-Eldin A, Törrönen AR. Identification and quantification of phenolic compounds in berries of Fragaria and Rubus species (family rosaceae). J Agric Food Chem. 2004;52:6178–87.
43. Mattila P, Hellström J, Törrönen R. Phenolic acids in berries, fruits, and beverages. J Agric Food Chem. 2006;54:7193–9.
44. Shidfar F, Heydari I, Hajimiresmaiel SJ, Hosseini S, Shidfar S, Amiri F. The effects of cranberry juice on serum glucose, apoB, apoA-I, Lp(a), and paraoxonase-1 activity in type 2 diabetic male patients. J Res Med Sci. 2012;17:355–60.
45. Torronen R, Kolehmainen M, Sarkkinen E, Poutanen K, Mykka H, Niskanen L. Berries Reduce Postprandial Insulin Responses to Wheat and Rye Breads in Healthy Women 1 – 4. J Nutr. 2013;143:430–6.

46. Lee IT, Chan YC, Lin CW, Lee WJ, Sheu WHH. Effect of cranberry extracts on lipid profiles in subjects with type 2 diabetes. Diabet Med. 2008;25:1473–7.
47. Novotny JA, Baer DJ, Khoo C, Gebauer SK, Charron CS. Cranberry juice consumption lowers markers of cardiometabolic risk, including blood pressure and circulating C-reactive protein, triglyceride, and glucose concentrations in adults. J Nutr. 2015;145:1185–93.
48. Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong C, Nettleton JA, et al. Flavonoid intake and cardiovascular disease mortality : a prospective study in postmenopausal women 1 – 4. Am J Clin Nutr. 2007;86:895–909.
49. Hertog MGL, Kromhout D, Aravanis C, Ratko Buzina M, Flaminio Fidanza, MD; Simona Giampaoli, MD; Annemarie Jansen, RD; Alessandro Menotti M, Nedeljkovic S, et al. Flavonoid Intake and Long-term Risk of Coronary Heart Disease and Cancer in the Seven Countries Study. Arch Intern Med. 1995;155:381–6.
50. Monteiro MMO, França-Silva MS, Alves NFB, Porpino SKP, Braga VA. Quercetin improves baroreflex sensitivity in spontaneously hypertensive rats. Molecules. 2012;17:12997–3008.
51. Ciocoiu M, Badescu L, Miron A, Badescu M. The involvement of a polyphenol-rich extract of black chokeberry in oxidative stress on experimental arterial hypertension. Evidence-based Complement Altern Med. 2013;2013.
52. Mackraj I, Govender T, Ramesar S. The antihypertensive effects of quercetin in a salt-sensitive model of hypertension. J Cardiovasc Pharmacol. 2008;51:239–45.
53. Perez-Vizcaino F, Duarte J, Jimenez R, Santos-Buelga C, Osuna A. Antihypertensive effects of the flavonoid quercetin. [Review] [48 refs]1226. Pharmacol Reports PR. 2009;61:67–75.
54. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men. Br J Nutr. 2008 Feb;99:352–9.
55. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA. 2006;296:1255–65.
56. Liu L, Nettleton J a, Bertoni AG, Bluemke D a, Szklo M. Dietary pattern, the metabolic syndrome, and left ventricular mass and systolic function: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr. 2009;90:362–8.
57. Janszky I, Mukamal KJ, Ljung R, Ahnve S, Ahlbom A, Hallqvist J. Chocolate consumption and mortality following a first acute myocardial infarction: The Stockholm Heart Epidemiology Program. J Intern Med. 2009;266:248–57.

58. Prior RL, Cao G, Martin A, Sofic E, Mcewen J, Brien CO, et al. Antioxidant capacity as influenced by total phenolic and anthocyanin content, maturity , and variety of Vaccinium Species. J Agric Food Chem. 1998;8561:2686–93.
59. Neto CC. Cranberry and blueberry: Evidence for protective effects against cancer and vascular diseases. Mol Nutr Food Res. 2007;51:652–64.
60. Ahuja JKC, Haytowitz DB, Pehrsson PR, Roseland J, Exler J, Khan M, et al. Composition of Foods Raw , Processed , Prepared USDA National Nutrient Database for Standard Reference , Release 27 Documentation and User Guide. US Dep Agric Agric Res Serv Beltsv Hum Nutr Res Cent Nutr Data Lab. 2013;2:1–136.
61. Lazzè MC, Pizzala R, Perucca P, Cazzalini O, Savio M, Forti L, et al. Anthocyanidins decrease endothelin-1 production and increase endothelial nitric oxide synthase in human endothelial cells. Mol Nutr Food Res. 2006;50:44–51.
62. Xu JW, Ikeda K, Yamori Y. Upregulation of endothelial nitric oxide synthase by cyanidin-3-glucoside, a typical anthocyanin pigment. Hypertension. 2004;44:217–22.
63. Kalea AZ, Clark K, Schuschke DA, Klimis-Zacas DJ. Vascular reactivity is affected by dietary consumption of wild blueberries in the Sprague-Dawley rat. J Med Food. 2009;12:21–8.
64. Shaughnessy KS, Boswall IA, Scanlan AP, Gottschall-Pass KT, Sweeney MI. Diets containing blueberry extract lower blood pressure in spontaneously hypertensive stroke-prone rats. Nutr Res. 2009;29:130–8.
65. Erlund I, Koli R, Alfthan G, Marniemi J, Puukka P, Mustonen P, et al. Favorable effects of berry consumption on platelet function , blood. Am J Clin Nutr. 2008;87:323–31.
66. Novotny JA, Baer DJ, Khoo C, Gebauer SK, Charron CS. Cranberry juice consumption lowers markers of cardiometabolic risk, including blood pressure and circulating C-reactive protein, triglyceride, and glucose concentrations in adults. J Nutr. 2015 Jun;145:1185–93.
67. Leiro J, Arranz JA, Fraiz N, Sanmartı ML. Effect of cis -resveratrol on genes involved in nuclear factor kappa B signaling. Int Immunopharmacol. 2005;5:393–406.
68. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart Disease and Stroke Statistics — 2008 Update A Report From the American Heart Association Statistics Committee and. 2015;
69. Ross R. Atherosclerosis—An inflammatory disease. N Engl J Med. 1999;340:115–26.
70. Robbesyn F, Salvayre R, Negre-salvayre A. Dual Role of Oxidized LDL on the NF-KappaB Signaling Pathway. Free Radic Res. 2004;38:541–51.

71. Klouche M, May AE, Hemmes M, Meßner M, Kanse SM, Preissner KT, et al. Enzymatically modified, nonoxidized LDL induces selective adhesion and transmigration of monocytes and T-lymphocytes through human endothelial cell monolayers. Arter Thromb Vasc Biol. 1999;19:784–93.
72. Brewer Junior H. Focus on high-density lipoproteins in reducing cardiovascular risk. Am Hear J. 2004;148:S14–8.
73. Barter P, Kastelein J, Nunn A, Hobbs R, Forum F. High density lipoproteins (HDLs) and atherosclerosis ; the unanswered questions. Atherosclerosis. 2003;168:195–211.
74. Chen H, Zuo Y, Deng Y. Separation and determination of flavonoids and other phenolic compounds in cranberry juice by high-performance liquid chromatography. J Chromatogr A. 2001;913:387–95.
75. Wang PL, Du CT, Francis FJ. Isolation and characterization of polyphenolic in cranberries. J Food Sci. 1978;43:1402–4.
76. Wang Y, Catana F, Yang Y, Roderick R, Breemen RB Van. An LC-MS method for analyzing total resveratrol in grape juice, cranberry juice, and in wine. J Agric Food Chem. 2002;50:431–5.
77. Nickel T, Schmauss D, Hanssen H, Sicic Z, Krebs B, Jankl S, et al. oxLDL uptake by dendritic cells induces upregulation of scavenger-receptors, maturation and differentiation. Atherosclerosis. 2009;205:442–50.
78. Reed J. Cranberry Flavonoids, Atherosclerosis and Cardiovascular Health. Crit Rev Food Sci Nutr. 2002;42:301–16.
79. Peng C, Liu L, Chuang C, Chyau C, Huang C, Wang C. Mulberry water extracts possess an anti-obesity effect and ability to inhibit hepatic lipogenesis and promote lipolysis. J Agric Food Chem. 2011;59:2663–71.
80. Prior RL, Wu X, Gu L, Hager T, Hager A, Wilkes S, et al. Purified berry anthocyanins but not whole berries normalize lipid parameters in mice fed an obesogenic high fat diet. Mol Nutr Food Res. 2009;53:1406–18.
81. Xia X, Ling W, Ma J, Xia M, Hou M, Wang Q, et al. An Anthocyanin-Rich Extract from Black Rice Enhances Atherosclerotic Plaque Stabilization in Apolipoprotein E – Deficient Mice 1. J Nutr. 2006;136:2220–5.
82. Curtis PJ, Kroon PA, Hollands WJ, Walls R, Jenkins G, Kay CD, et al. Cardiovascular disease risk biomarkers and liver and kidney function are not altered in postmenopausal women after ingesting an elderberry extract rich in anthocyanins for 12 weeks. J Nutr. 2009;139:2266–71.

83. Karlsen A, Retterstøl L, Laake P, Paur I, Kjølsrud-bøhn S, Sandvik L, et al. Anthocyanins Inhibit Nuclear Factor- k B Activation in Monocytes and Reduce Plasma Concentrations of Pro-Inflammatory Mediators in Healthy Adults 1 – 3. J Nutr. 2007;137:1951–4.
84. Couillard C, Ruel G, Archer WR, Pomerleau S, Bergeron J, Couture P, et al. Circulating Levels of Oxidative Stress Markers and Endothelial Adhesion Molecules in Men with Abdominal Obesity. J Clin Endocrinol Metab. 2005;90:6454–9.
85. Kume N, Cybulsky M, Gimbrone MA. Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. J Clin Invest. 1992;90:1138–44.
86. Duthie G, Kyle J, Jenkinson A, Duthie S, Baxter G, Paterson J. Increased Salicylate Concentrations in Urine of Human Volunteers after Consumption of Cranberry Juice. J Agric Food Chem. 2005;53:2897–900.
87. Eisele G, Schwedhelm E, Schieffer B, Tsikas D, Böger R. Acetylsalicylic acid inhibits monocyte adhesion to endothelial cells by an antioxidative mechanism. J Cardiovasc Pharmacol. 2004;43:514–21.
88. Ruel G, Pomerleau S, Couture P, Lamarche B, Couillard C. Changes in plasma antioxidant capacity and oxidized low-density lipoprotein levels in men after short-term cranberry juice consumption. Metabolism. 2005;54:856–61.
89. Festa, A.; D'Agostino, R.; Jr Howard, G.; Mykkanen, L.; Tracy, R. P.; Haffner SM. Chronic Subclinical Inflammation as Part of the Insulin Resistance Syndrome : The Insulin Resistance Atherosclerosis Study (IRAS). Circ J Am Hear Assoc. 2000;102:42–7.
90. Santos A-C, Lopes C, Guimarães JT, Barros H. Central obesity as a major determinant of increased high-sensitivity C-reactive protein in metabolic syndrome. Int J Obes (Lond). 2005;29:1452–6.
91. Lopez-Miranda J, Ordovas JM, Ostos MA, Marin C, Jansen S, Salas J, et al. Dietary fat clearance in normal subjects is modulated by genetic variation at the apolipoprotein B gene locus. Arterioscler Thromb Vasc Biol. 1997;17:1765–73.
92. McCarty MF. Nitric oxide deficiency, leukocyte activation, and resultant ischemia are crucial to the pathogenesis of diabetic retinopathy/neuropathy - Preventive potential of antioxidants, essential fatty acids, chromium, ginkgolides, and pentoxifylline. Med Hypotheses. 1998;50:435–49.
93. Tsopanakis C, Tsopanakis A. Stress hormonal factors, fatigue, and antioxidant responses to prolonged speed driving. Pharmacol Biochem Behav. 1998;60:747–51.
94. Halliwell B, Gutteridge JM. Free Radicals in Biology and Medicine. Fourth. Oxford University Press; 2007;

95. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? Free Radic Biol Med. 2010;49:1603–16.
96. Ruel G, Couillard C. Evidences of the cardioprotective potential of fruits: The case of cranberries. Mol Nutr Food Res. 2007;51:692–701.
97. Halliwell B. Effect of diet on cancer development: is oxidative DNA damage a biomarker? Free Radic Biol Med. 2002;32:968–74.
98. Wojdyło A, Oszmiański J, Bober I. The effect of addition of chokeberry, flowering quince fruits and rhubarb juice to strawberry jams on their polyphenol content, antioxidant activity and colour. Eur Food Res Technol. 2008;227:1043–51.
99. Veberic R, Jakopic J, Stampar F, Schmitzer V. European elderberry (Sambucus nigra L.) rich in sugars, organic acids, anthocyanins and selected polyphenols. Food Chem. 2009;114:511–5.
100. Hollands W, Brett GM, Radreau P, Saha S, Teucher B, Bennett RN, et al. Processing blackcurrants dramatically reduces the content and does not enhance the urinary yield of anthocyanins in human subjects. Food Chem. 2008;108:869–78.
101. Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem. 2006;54:4069–75.
102. Manach C, Scalbert A, Morand C et al. Bioavailability, Polyphenols: Food sources and. Am J Clin Nutr. 2004;79:727–47.
103. Kroon PA, Clifford MN, Crozier A, Day AJ, Donovan JL, Manach C, et al. How should we assess the effects of exposure to dietary polyphenols in vitro? Am J Clin Nutr. 2004;80:15–21.
104. Netzel M, Strass G, Kaul C, Bitsch I, Dietrich H, Bitsch R. In vivo antioxidative capacity of a composite berry juice. Food Res Int. 2002;35:213–6.
105. Wojdyło A, Figiel A, Oszmiański J. Effect of drying methods with the application of vacuum microwaves on the bioactive compounds, color, and antioxidant activity of strawberry fruits. J Agric Food Chem. 2009;57:1337–43.
106. Srivastava A, Akoh CC, Yi W, Fischer J, Krewer G. Effect of storage conditions on the biological activity of phenolic compounds of blueberry extract packed in glass bottles. J Agric Food Chem. 2007;55:2705–13.
107. Hartmann A, Patz C-D, Andlauer W, Dietrich H, Ludwig M. Influence of processing on quality parameters of strawberries. J Agric Food Chem. 2008;56:9484–9.
108. Ggsiorowskia K, Szyba K, Brokosa B, Kolaczyliska B, Jankowiak-wlodarczyk M, Oszmiafiski J. Antimutagenic activity of anthocyanins isolated from Aronia melanocarpa fruits. 1997;119:37–46.

109. Youdim K, Martin A, Joseph J. Incorporation of the elderberry anthocyanins by endothelial cells increases protection against oxidative stress. Free Radic Biol Med. 2000;29:51–60.
110. Youdim KA, Mcdonald J, Kalt W, Joseph JA. Potential role of dietary flavonoids in reducing microvascular endothelium vulnerability to oxidative and inflammatory insults. J Nutr Biochem. 2002;13:282–8.
111. Duthie SJ, Gardner PT, Morrice PC, Wood SG, Bestwick CC, Duthie GG. DNA stability and lipid peroxidation in vitamin E-deficient rats in vivo and colon cells in vitro--modulation by the dietary anthocyanin, cyanidin-3-glycoside. Eur J Nutr. 2005;44:195–203.
112. Kamei H, Koide T, Kojimam T, Hasegawa M, Terabe K, Umeda T, et al. Flavonoid-Mediated Tumor Growth Suppression Demonstrated by in vivo Study. Cancer Biother Radiopharm. 2009;11:193–6.
113. Hakimuddin F, Paliyath G, Meckling K. Selective cytotoxicity of a red grape wine flavonoid fraction against MCF-7 cells. Breast Cancer Res Treat. 2004;85:65–79.

5.2 ARTIGO 2:

Cranberry Juice Decreases Disease Activity and Improves Prognosis in Patients with Rheumatoid Arthritis

Nataly Simões Bandiera Thimóteo[1], M.Sc, Daniela Frizon Alfieri[1] M.Sc, Brunna Emanuella França Rego[1], M.Sc, Bruna Miglioranza Scavuzzi[1], PhD, Elis Carolina de Souza Fatel[2], PhD, Marcell Alysson Batisti Lozovoy[1,3], PhD, Andréa Name Colado Simão[1,3], PhD, and Isaias Dichi[4*], MD, PhD

Effects of cranberry juice on Rheumatoid Arthritis

[1] Research Laboratory in Applied Immunology – University of Londrina, Brazil.

[2] Department of Nutrition – Universidade Federal Fronteira Sul, Brazil.

[1,3]Department of Pathology, Clinical Analysis and Toxicology – University of Londrina, Brazil.

[4] Department of Internal Medicine – University of Londrina, Brazil.

NSBT was responsible for recruiting the patients, interpretation of the results and the writing of the manuscript. DFA, BEFR, BMS, ECSF and MABL were responsible for recruiting the patients and the laboratorial analysis. ANCS was responsible for the study design, interpretation of the results and the writing of the manuscript. ID was responsible for the original concept of the study, the study design, interpretation of the results and the writing of the manuscript. All authors read and approved the final manuscript.

The manuscript has: 4626 words, 03 tables and 02 figures.

*Corresponding author: Isaias Dichi, MD, PhD

Postal address: Department of Internal Medicine. Robert Koch Avenue nº 60 Bairro Cervejaria, University of Londrina. Londrina, Paraná, Brazil. CEP: 86038-440 Tel: (55) 43 3371 2234; Fax: +55-43-3371-2619

E-mail: dichi@sercomtel.com.br

ABSTRACT

Backgrond: Studies have shown that cranberry (*Vaccinium macrocarpon*) has antiinflammatory and antioxidant effects, however, the effects of cranberry juice consumption has not been studied in patiens with rheumatoid arthritis (RA). Objective: Thus, the aim of this study was to verify the effect of cranberry juice consumption on various inflammatory, metabolic biomarkers, and on the disease activity in patients with RA. Research Methods & Procedures: A prospective study was conducted with 41 female patients diagnosed with RA. The disease activity measured by DAS28 (Disease Activity Score 28) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, and several inflammatory and biochemical biomarkers were analyzed. The first group (control group, n = 18) maintained the usual diet, the second group (cranberry group, n = 23) consumed 500mL / day of low calorie cranberry juice. Results: Regarding the baseline values, the group who received the cranberry juice intervention presented a decrease in the values of DAS 28 ($p = 0.048$) and anti-CCP ($p = 0.034$) after 90 days of treatment, whereas changes in inflammatory biomarkers were not found. Conclusion: The present study indicates that cranberry juice decreased disease activity and improved prognosis and therefore have beneficial effects in RA patients.

Keywords: cranberry, inflammation, bioactive compounds, polyphenols, rheumatoid arthritis.

INTRODUCTION

The term rheumatoid arthritis (RA) was described more than 150 years 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 as well as by extra-articular involvement and is thus classified as a systemic inflammatory disease. The disorder likely develops from individuals who are genetically susceptible to abnormal immune responses and 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 last 40 years, the prevalence of RA has not decreased, and life expectancy for patients with RA is significantly lower than that of the heathy population [3, 4], being women three times more likely to be affected than men [5].

Patients with RA have one-third to one half of the causes of early mortality due to cardiovascular diseases (CVD), 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 been demonstrated, as well as in other aspects related to the pathogenesis of RA [8], suggesting that these antioxidants effectively suppress the release of inflammatory cytokines, thereby decreasing reactive oxigen species (ROS) [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 in 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]. While 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 1 (IL-1) and interleukin 6 (IL-6) in patients with metabolic syndrome [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, disease activity, and prognosis in RA patients.

MATERIALS AND METHODS

Patients

This study included 41 women with RA patients. The intervention and the control group had 23 and 18 participants, respectively. Patients with RA were selected from among the ambulatory of Rheumatology of the University Hospital of Londrina, Paraná, Brazil. None of the participants in the study presented heart, thyroid, renal, hepatic, gastrointestinal, oncological diseases or other autoimmune disease, and none were receiving estrogen replacement therapy or antioxidant supplements. Also, patients with renal impairment, B12 insufficiency, hypothyroidism and hemolysis or using drugs, such as phenytoin, isoniazid, methotrexate and L-dopa were excluded from the study to avoid interference with homocysteine results[18]. All of the individuals did not drink alcohol regularly. Patients who were taking antihypertensive drugs were not excluded and were allowed to continue taking the same dose of the drugs. None of the subjects followed a specific diet before the study began. The patients were instructed by a nutritionist 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 human subjects/patients were approved by the University of Londrina Paraná, Brazil. Written informed consent was obtained from all patients. The Ethical Committee of the University of Londrina, Paraná, Brazil approved all procedures involving human participants (CAAE: 13426014.6.0000.5231).

Study Design

In this prospective study, patients with RA were assigned to one of two groups after stratification by age and waist circumference (WC): the first group (control group - C, n=18) was only directed to maintain their usual diet, while the second group (low calorie cranberry juice, n=23) ingested 500 mL/d of reduced-energy cranberry juice. All of the groups were evaluated at the beginning of the study and after 90 days. Interviews were performed to assure no change in lifestyle factors had happened throughout the study. The nutrient composition of 500 mL of cranberry juice was as follows: 50 Kcal, 0 g of protein, 12.5g of carbohydrate, 0 g of lipids, 0 g of fiber, 75 mg of sodium, vitamin C 150 mg, 131.92 mg

of proanthocyanidins, total phenolics of 258.75 mg, and 0.30 mg of folic acid.. Evaluation of clinical and laboratorial parameters was assessed at the beginning of the study and after 90 days.

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. Subjects were asked to bring back any unconsumed juice to assess unmonitored compliance. In addition, telephone interviews were performed to evaluate if the patients were correctly using the supplement and the patients were recommended to avoid lifestyle changes.

Treatment adhesion of the participants of the study was approximately 95%.

Clinical Evaluation

Information on medical history was obtained in the clinical evaluation performed by a rheumatologist. Information on the the use of medications, including non-steroidal anti-inflammatory 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 by using an electronic scale, with individuals wearing light clothing and no shoes; height was measured to the nearest 0.1 cm by using a stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Patients were selected according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [19], and disease activity status was determined using the 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 analogue scale where 0=best, 100=worst), plus levels of erythrocyte sedimentation rate (ESR) (mg/L).

Biochemical and immunological biomarkers

After fasting for 12 hours, venous blood was withdrawn with Ethylene Diamine Tetra acetic acid (EDTA) coated sterile tubes (BD Vacutainer® UltraTouch™, Franklin Lakes, NJ, EUA). Whole blood was allowed to stand for 30 min and then was centrifuged at 1500 rpm for 10 min. Plasma and serum samples were separated, divided into aliquots and stored at -80ºC for subsequent analysis.

Total cholesterol, HDL, LDL, triacylglycerol, and glucose levels were evaluated by a biochemical auto-analyzer (Dimension Dade AR Dade Behring, Deerfield, IL, USA) using Dade Behring® kits. Insulin analysis was performed by microparticle enzyme-linked immunoassay (MEIA) using ABBOTT® AXSYM equipment. Homeostatic Model Assessment (HOMA) is an estimate of insulin resistance (IR) [20] and was calculated using the following formula: HOMA-IR = fasting glucose (mmol/L) x fasting insulinemia (mU/L)/22.5.

White blood cell, platelet, and ESR counts were determined using hematological autoanalyzers. Serum CRP levels were measured using a turbidimetric assay (C8000, ABBOTT, Architect Abbott Laboratories, Abbott Park, IL, USA). Serum ferritin levels were determined with a chemiluminescent microparticle assay (Architect, Abbott Laboratory, Abbott Park, IL, USA). Rheumatoid Factor titers were measured using a turbidimetric assay (C8000, ABBOTT, Architect Abbot Laboratories, Abbott Park, IL, USA) and the results were expressed as U/mL. Anti-cyclic citrullinated peptide (anti-CCP) antibodies were tested using a chemiluminescent microparticle immunoassay (Architect, Abbott Laboratory, Abbott Park, IL, USA), and the results were expressed as U/mL. Total plasma levels of homocysteine were measured by chemiluminescence (ARCHITECT; Abbott Laboratory).

Statistical analyses

Categorical data were analyzed by Fisher's exact test or the chi-squared 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 25–75 percentiles. All statistical analyses were performed using the IBM SPSS, version of Windows 24. The tests were two-tailed and an alpha level of 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 Cal Stat program was used to calculate the sample size, based on mean and standard deviation for some of the parameters previously evaluated in other studies.

RESULTS

Non-compliance was verified in three patients from the intervention group. The demographical and clinical characteristics of the patients are presented in table 1. There was no difference between groups regarding age, ethnicity, smoking habits, extra-articular signs and drug treatments.

Table 1 – Demographic and clinical characteristics in the control group and cranberry juice group of patients with rheumatoid arthritis (RA) at the baseline.

	Control (n=18)	**Cranberry (n=20)**	**P**
Age (years)	50.5 (40.0-60.0)	55 (51.00-65.00)	0.221
Ethnicity (C/NC)	16 (88.9%)/ 2(11.1%)	17 (85.0%)/ 3(15.0%)	0.723
Tabagism (yes)	2 (11,1%)	0 (0.0%)	0.126
Physical activity (yes)	5 (27.8%)	5 (25.0%)	0.846
Extra articular (yes)	0 (0.0%)	3 (15.0%)	0.087
Metotrexate	10 (62.5%)	14 (70.0%)	0.635
Prednisone	14 (77.7%)	16(80.0%)	0.365
Hydroxychloroquine	8 (50.0%)	6 (30.0%)	0.221

Data are shown in median and interquartile range (25% -75%) and absolute number (n) and percentage (%). Categorical data were analyzed with the chi-square or Fisher's exact test. Continuous data were analyzed with the Mann Withney test.

The parameters related to metabolic components presented by patients at baseline and after 90 days are shown in table 2. HDL levels were higher in the cranberry group compared to the control group at the beginning of the study. An increase in the values for fasting glucose were observed ($p = 0.04$), both in the control and the intervention groups. There were no statistically significant differences in relation to inter-group changes

Table 2: Evaluation of the metabolic components of the control and cranberry groups presented at baseline and after 90 days.

	Control (n=18)			Cranberry (n=20)			
	T0[A]	**T90**	**p**	**T0[B]**	**T90**	**p**	**p [AXB]**
Body mass index (kg/m^2)	30.0 (22.0-32.0)	29.5 (22.0-32.0)	NS	26.0 (23.0-30.0)	27.0 (26.5-30.0)	NS	NS
Abdominal circumference (cm)	104.0 (91.0-110.0)	104.0 (90.0-109.0)	NS	97.0 (81.0-103.0)	96.5 (84.5-107.0)	NS	NS
HDL (mg/dl)	54.5 (48.0-59.0)	51.0 (48.0-64.0)	NS	64.5 (51.5-80.0)	63.0 (49.0-79.5)	NS	0.044
LDL (mg/dl)	129.0 (94.0-149.0)	128.0 (97.0-140.0)	NS	109.0 (88.0-136.0)	115.0 (90.0-125.5)	NS	NS
Total cholesterol (mg/dl)	204.0 (174.0-234.0)	200.5 (178.0-233.0)	NS	207.0 (183.0-219.5)	204.5 (183.0-224.5)	NS	NS
Triglycerides (mg/dl)	101.5 (72.0-154.0)	100.0 (80.0-172.0)	NS	120.0 (87.0-135.5)	115.0 (80.5-150.5)	NS	NS
Glucose (mg/dl)	84.5 (77.0-92.0)	93.0 (88.0-102.0)	0.04	89.5 (81.0-96.5)	94.0 (90.0-106.0)	0.04	NS
Insulin (mU/l)	8.80 (5.90-13.7)	8.3 (5.60-14.6)	NS	8.5 (7.4-12.25)	8.0 (5.7-12.6)	NS	NS
HOMA-IR (unid)	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 (mmol/ml)	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; LDL, low density lipoprotein; HOMA-IR, Homeostasis Model Assessment insulin resistance, abdominal circimference, body mass index.
Data are shown in median and interquartile range (25% -75%). The Wilcoxon test was performed to verify changes from baseline (intra-group changes). The Mann-Whitney test was performed to compare differences between the baseline values and across treatment groups (inter-group changes). NS, non-significant; **[AxB]** – differences between baselines.

Table 3 shows the parameters related to disease activity and inflammatory status in the patients at the beginning of the study and after 90 days in the control and the cranberry groups. There were no differences at the baseline values between the groups. At the end of the 90-day treatment period compared to baseline values, the cranberry juice intervention group showed a significant reduction in DAS 28 ($p = 0.048$) and in anti-CCP levels ($p = 0.034$). There were no statistically significant differences in relation to inter-group changes.

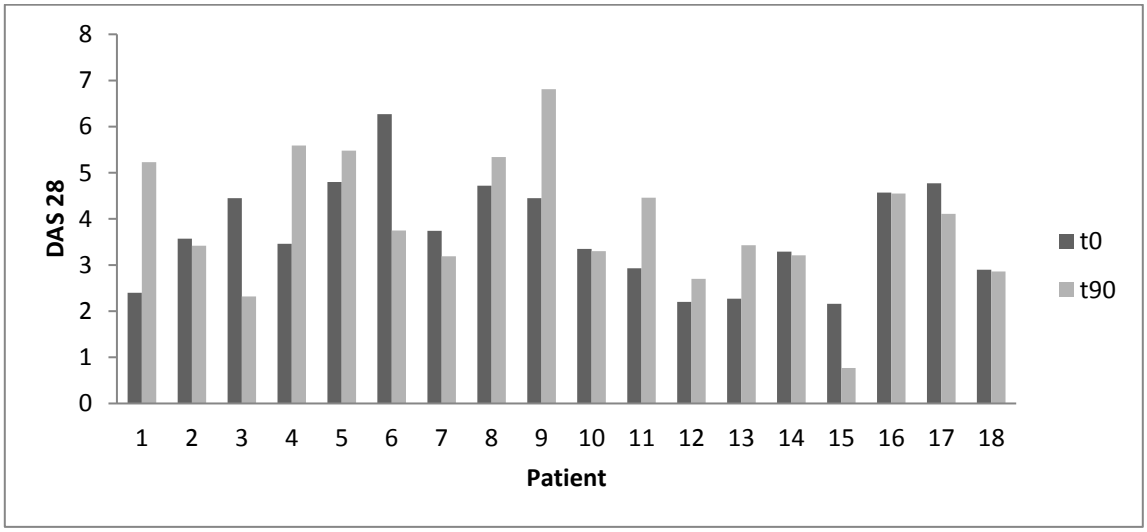
Table 3: Evaluation of the disease activity and inflammatory components of the control and cranberry groups presented at the beginning of the study and after 90 days.

	Control (n=18)			Cranberry (n=20)			
	T0^{A}	**T90**	**p**	**T0^{B}**	**T90**	**p**	**p ^{AXB}**
DAS 28	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 (U/mL)	6.0 (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
Rheumatoid factor (Ui/mL)	19.7 (13.5-49.3)	32.25 (4.1-54.9)	NS	7.55 (4.2-44.95)	7.0 (3.65-59.4)	NS	NS
ESR (mm/h)	32.5 (12.0-40.0)	20.0 (15.0-42.0)	NS	18.5 (6.0-32.45)	22.0 (5.0-33.0)	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 (Leu/mm^3)	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 (µ/L)	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

DAS, disease activity index; anti-CCP, anti-cyclic citrullinated peptide antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NS, non-significant.
Data are shown in median and interquartile range (25% -75%). The Wilcoxon test was performed to verify changes from baseline (intra-group changes). The Mann-Whitney test was performed to compare differences between the baseline values and across treatment groups (inter-group changes). NS, non-significant; **^{AxB} –** differences between baselines.

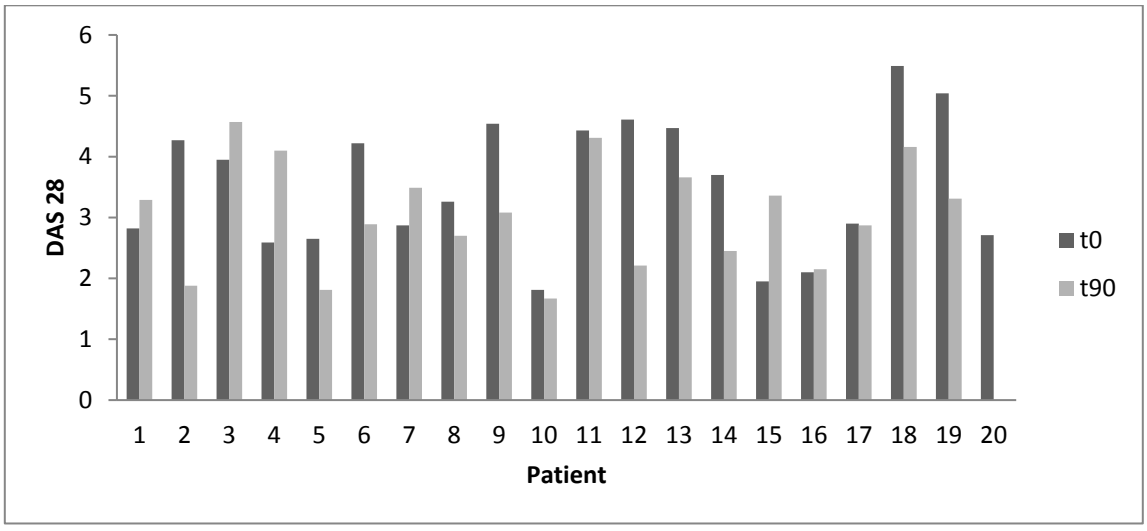
Figure 1 and Figure 2 illustrates DAS 28-ESR of each patient at the baseline and after 90 days in the cranberry and control groups, respectively. Individualized analysis showed that ten patients decreased DAS 28 after cranberry ingestion (numbers 2,5,6,8,9,12,13,14,18,19). In contrast five patients increased DAS 28 (numbers 1,3,4,7,15) and five patients maintained their values (numbers 10, 11, 16, 17, 20). On the other hand, in the control group ten patients maintained DAS 28 (numbers 2,5,7,8,10,12,14,16,17,18), whereas five increased (numbers 1,4,9,11,13) and three reduced their values (numbers 3,6,15).

Figure 1: Disease activity in the eighteen patients of the control group at the beginning of the study (T0) and after 90 days (T90).



DAS, disease activity status.

Figure 2: Disease activity in the twenty patients who used cranberry at the beginning of the study (T0) and after 90 days (T90).



DAS, disease activity status.

DISCUSSION

The main findings of this study confirm the hypothesis that daily consumption of 500 mL of cranberry juice daily promotes an improvement of disease activity and prognosis in women with RA. This effect was demonstrated by a significant decrease in the disease

activity score measured by DAS 28 as well as a significant decrease in anti-CCP levels, respectively.

Some types of autoantibodies act as markers for RA diagnosis, such as RF and several anti-citrullinated protein/peptide antibodies (ACPA) 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, as it has a sensitivity of 70-75% and a specificity of about 95% [21]. 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 [21].

We are not aware of any study that has verified the effect of cranberry in RA patients. 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 DAS 28 and anti-CCP, without concomitant reduction in inflammatory status. However, some explanations can be suggested: 1st) the small number of participants; 2nd) no available information on the cytokine levels which were not performed and could give a deeper analysis of the inflammatory status; 3rd) no available information on oxidative stress which also contributes to RA pathophysiology and could even precede the inflammatory events [22].

ESR and CRP, although nonspecific, are tests frequently used to monitor disease activity. The disease activity index (DAS 28) 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 since 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 [23, 24]. Duffey & Sutherland [15] reported that cranberry juice consumers had lower CRP levels than non-consumers. Other study with healthy subjects also found a decrease in CRP with cranberry juice [16]. In contrast, other reports have not found any significant change in inflammatory markers with cranberry in patients with type 2 diabetes mellitus [25], coronary artery disease [26] and metabolic syndrome [27]. In a study performed by our group with metabolic syndrome patients, low-calorie cranberry juice (700 mL/d) given for two months 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 evidence that quercetin, a flavonoid present in large amounts in cranberries, is a potent down-regulator of the nuclear kappa B factor (NF-kB) pathway [28]. Additionally, quercetin has been shown to inhibit the activities of cyclooxygenase and lipoxygenase [28]. 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 CVD by modulating the NF-kB and JAK STAT3 pathways in cultured cells [29].

The following limitations have to be considered in the present study. First, the small number of participants since with a larger group, perhaps it would be possible to observe significant differences in more parameters. Second, the absence of a placebo control group, although a similar design has been previously used in several studies [30–33]. Nevertheless, the present study also has several strengths. First, to our knowledge, this is the first study to evaluate patients with rheumatoid arthritis using cranberry juice. Second, as only women were selected, a greater homogeneity in the results was obtained. Third, we rigorously tried to assure that the patients did not take any drug or presented any disease, which could interfere with the results. Fourth, although several features of DAS-28, 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.

In summary, 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 opportunities for the management of RA, as a dietary supplementation, although this is the first study to investigate consumption of cranberries in patients with RA. 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.

FINANCIAL SUPPORT

This research was supported by the National Research Council of Brazil - CNPq. Juxx Company supplied the cranberry juice. The Juxx Company had no role in the design, analysis, or writing of this article.

Declarations of interest: none.

Acknowledgements: NSBT: conception and design of the study; collection, analysis and interpretation of data; drafting the manuscript; approval of the final version of the manuscript. DFA, BEFR, BMS, EF, MABL: collection, analysis and interpretation of data; drafting the manuscript; approval of the final version of the manuscript. ANCS, ID: conception and design of the study; interpretation of data; drafting the manuscript; approval of the final version of the manuscript.

REFERENCES

[1] Garrod, AB. The nature and treatment of gout and rheumatic gout. 1st ed. London: Walt and Maberly;1859.

[2] Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med 2011;183:372–8. doi:10.1164/rccm.201004-0622OC.

[3] Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, et al. Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years. Arthritis Rheum 2003;48:54–8. doi:10.1002/art.10705.

[4] Minaur NJ, Jacoby RK, Cosh JA, Taylor G, Rasker JJ. Outcome after 40 years with rheumatoid arthritis: a prospective study of function, disease activity, and mortality. J Rheumatol 2004;69:3–8.

[5] Spector TD. Rheumatoid arthritis. Rheum Dis Clin North Am 1990;16:513–37.

[6] Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. Arthritis Rheum 2008;59:1690–7. doi:10.1002/art.24092.

[7] Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol 2015;11:390–400. doi:10.1038/nrrheum.2015.40.

[8] Riccioni G, Bucciarelli T, Mancini B, Corradi F, Di Ilio C, Mattel PA, et al. Antioxidant vitamin supplementation in cardiovascular diseases. Ann Clin Lab Sci 2007;37:89–95. doi:10.1517/13543784.16.1.25.

[9] Surh YJ, Kundu JK, Na HK, Lee JS. Redox-sensitive transcription fators as prime targets for chemoprevention with antiinflammatory and antioxidant phytochemicals. J Nutr 2005;135:2993S–3001S. doi:10.1093/jn/135.12.2993S.

[10] Dorothy J, Pattison RAH, Pattison DJ, Harrison RA, Symmons DPM. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. J Rheumatol 2004;31:1310–9. doi:15229949.

[11] Basu A , Lyons TJ. Berries in the nutritional management of metabolic syndrome. In: Dichi I, Simão ANC, editors. Nutritional Intervention in Metabolic Syndrome, Boca Raton, Florida: CRC Press Book; 2015, p. 345-52.

[12] Reed J. Cranberry flavonoids, atherosclerosis and cardiovascular health. Crit Rev Food Sci Nutr 2002;42:301–16. doi:10.1080/10408390209351919.

[13] Blumberg JB, Basu A, Krueger CG, Lila MA, Neto CC, Novotny JA, et al. Impact of Cranberries on Gut Microbiota and Cardiometabolic Health: Proceedings of the Cranberry Health Research Conference 2015. Adv Nutr 2016;7:759S–770S. doi:10.3945/an.116.012583.

[14] Blumberg JB, Camesano TA, Cassidy A, Kris-etherton P, Howell A, Manach C, et al. Cranberries and Their Bioactive Constituents in Human Health. Adv Nutr 2013;4:618–32. doi:10.3945/an.113.004473.

[15] Duffey KJ, Sutherland LA. Adult consumers of cranberry juice cocktail have lower C-reactive protein levels compared with nonconsumers. Nutr Res 2015;35:118–26. doi:10.1016/j.nutres.2014.11.005.

[16] Novotny JA, Baer DJ, Khoo C, Gebauer SK, Charron CS. Cranberry juice consumption lowers markers of cardiometabolic risk, including blood pressure and circulating C-reactive protein, triglyceride, and glucose concentrations in adults. J Nutr 2015;145:1185–93. doi:10.3945/jn.114.203190.

[17] Simão TNC, Lozovoy MAB, Simão ANC, Oliveira SR, Venturini D, Morimoto HK, et al. Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome. Br J Nutr 2013;110:1885–94. doi:10.1017/S0007114513001207.

[18] Panunzio MF, Pisano A, Antoniciello A, Di V, Frisoli L, Cipriani V, et al. Supplementation with fruit and vegetable concentrate decreases plasma homocysteine levels in a dietary controlled trial. Nutr Res 2003;23:1221–8. doi:10.1016/S0271-5317(03)00133-7.

[19] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8. doi:10.1136/ard.2010.138461.

[20] Haffner SM. Insulin resistance, inflammation and the prediabetic state. Am J Cardiol 2003;92:18-26J.

[21] Visser H. Ealy diagnosis of rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005;19:55–72. doi:10.1016/j.berh.2004.08.005.

[22] Jeon CH, Ahn JK, Chai JY, Kim HJ, Bae EK, Park SH, et al. Hypoxia appears at pre-arthritic stage and shows co-localization with early synovial inflammation in collagen induced arthritis. Clin Exp Rheumatol 2008;26:646–8.

[23] Rosa Neto NS, de Carvalho JF, Shoenfeld Y. Screening tests for inflammatory activity: Applications in rheumatology. Mod Rheumatol 2009;19:469–77. doi:10.1007/s10165-009-0211-z.

[24] Tamhane A, Redden DT, McGwin G, Brown EE, Westfall AO, Reynolds IV RJ, et al. Comparison of the disease activity score using erythrocyte sedimentation rate and C-reactive protein in African Americans with rheumatoid arthritis. J Rheumatol 2013;40:1812–22. doi:10.3899/jrheum.121225.

[25] Lee IT, Chan YC, Lin CW, Lee WJ, Sheu WHH. Effect of cranberry extracts on lipid profiles in subjects with type 2 diabetes. Diabet Med 2008;25:1473–7. doi:10.1111/j.1464-5491.2008.02588.x.

[26] Dohadwala MM, Holbrook M, Hamburg NM, Shenouda SM, Chung WB, Titas M, et al. Effects of cranberry juice consumption on vascular function in patients with coronary artery disease. Am J Clin Nutr 2011;93:934–40. doi:10.3945/ajcn.110.004242.

[27] Basu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. Nutr Res 2011;31:190–6. doi:10.1016/j.nutres.2011.02.003.

[28] Nijveldt RJ, Nood EV, Hoorn DEV, Boelens PG, Norren KV LP. Flavonoids: a Review of Probable Mechanisms of Action and Potential Applications. Am J Clin Nutr 2001;74:418. doi:10.1093/ajcn/74.4.418.

[29] McKay DL, Blumberg JB. Cranberries (Vaccinium macrocarpon) and cardiovascular disease risk factors. Nutr Rev 2007;65:490–502. doi:10.1301/nr.2007.nov.490.

[30] Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men. Br J Nutr 2008;99:352–9. doi:10.1017/S0007114507811986.

[31] Freedman JE., Parker C., Li L, Perlman JA., Frei B, Ivanov, V., et al. Select flavonoids and whole juice from purple grapes inhibit platelet function and enhance nitric oxide release. Circulation 2001;103:2792–8. doi:10.1161/01.CIR.103.23.2792.

[32] Keevil JV., Osman HE., Reed JD., Folts JD. Grape juice, but not orange juice or grapefruit juice, inhibits human platelet aggregation. J Nutr 2000;130:53–6. doi:10.1093/jn/130.1.53.

[33] O`Byrne DJ., Devaraj S., Grundy S, Jialal L. Comparison of the antioxidant effects of Concord grape juice flavonoids alpha-tocopherol on markers of oxidative stress in healthy adults. Am J Clin Nutr 2002;76:1367–74. doi:10.1093/ajcn/76.6.1367.

CONCLUSÃO

Os resultados da maioria dos estudos incluídos na revisão da literatura mostraram uma melhora em diversos parâmetros analisados da síndrome metabólica, e também elucidaram alguns mecanismos de ação envolvidos. Em resumo, as evidências científicas apontam que o consumo do cranberry pode conferir efeitos favoráveis nos componentes da síndrome metabólica. No entanto, ainda há poucos trabalhos disponíveis, sobretudo no que diz respeito aos mecanismos envolvidos. Dessa forma, são necessárias mais investigações para sustentar a recomendação do consumo de cranberry como intervenção nutricional para o tratamento da síndrome metabólica.

Este é o primeiro estudo que avalia o efeito da ingestão exclusiva de suco de cranberry de baixa caloria no processo de inflamação, presente na AR, bem como na atividade desta doença.

O presente estudo teve sua hipótese parcialmente confirmada sobre os efeitos benéficos com a ingestão de cranberry através da diminuição da atividade da doença em pacientes com AR. No entanto, não houve modificações nos biomarcadores inflamatórios. Esses achados podem abrir novos caminhos para analisar os efeitos do cranberry sobre a atividade da doença em pacientes com AR. Assim, mais pesquisas são necessárias para apoiar a recomendação do consumo de cranberry como uma intervenção nutricional para o tratamento da artrite reumatóide. Além disso, estudos são necessários para confirmar esses achados em pacientes do sexo masculino.

REFERÊNCIAS

ABELLA, V. et al. Review Article Adipokines, Metabolic Syndrome and Rheumatic Diseases. **Journal of Immunology Research**, v. 2014, p. 1–15, 2014.

ALBERTI, K. G. et al. International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. **Circulation**, v. 120, p. 1640–5, 2009.

ALETAHA, D. et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. **Arthritis Res Ther**, v. 7, p. R796-806, 2005.

ALETAHA, D. et al. Perception of improvement in patients with rheumatoid arthritis varies with disease activity levels at baseline. **Arthritis Rheum**, v. 61, n. 3, p. 313-20, 2009.

ALETAHA, D. et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. **Arthritis & Rheumatology**, v. 62, n. 9, p. 2569-81, 2010.

ALETAHA, D.; SMOLEN, J. S. The Simplifi ed Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. **Clin Exp Rheumatol**, v. 23, Suppl. 39, p. S100-8, 2005.

ANTONIADES, C. et al. Oxidative stress, antioxidant vitamins, and atherosclerosis. From basic research to clinical practice. **Herz**, v. 28, 628–38, 2003.

AVALOS, I. et al. Oxidative stress in systemic lúpus erithematosus: relationship to disease activity and symptom. **Lupus**, v. 16, n. 3, p. 195-200, 2007.

AZADBAKHT, L. et al. Soy consumption, markers of inflammation, and endothelial function: a cross-over study in postmenopausal women with the metabolic syndrome. **Diabetes Care**, v. 30, 967–73, 2007.

BASU, A. et al. Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. **J Am Coll Nutr**, v. 29, p. 31–40, 2010.

BASU, A. et al. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. **Nutr Res**, v. 31, n. 3, p. 190–6, mar. 2011.

BATAILLE, R.; KLEIN, B. C-reactive protein levels as a direct indicator of interleukin-6 levels in humans in vivo. **Arthritis Rheum**, v. 35, p. 982–4, 1992.

BERGER, M. M. Can oxidative damage be treated nutritionally? **Clin Nutr**, v. 24, n. 2, p. 172-83, 2005.

BÉRTOLO, M. B. et al. Atualização do consenso brasileiro no diagnóstico e tratamento da artrite reumatoide. **Revista Brasileira de Reumatologia**, São Paulo, v. 47 n. 3, maio/jun. 2009.

BICKERS, D. R.; ATHAR, M. “Oxidative stress in the pathogenesis of skin disease,” **The Journal of Investigative Dermatology**, v. 126, n. 12, p. 2565–75, 2006.

BIEMOND, A.; SWAAK, A. J. G.; KOSTER, J. F. Protective factors against oxygen free radicals and hydrogen peroxide in rheumatoid arthritis synovial fluid. **Arthr Rheum**, v. 27, p. 760–5, 1984.

Birben, E. et al. Oxidative Stress and Antioxidant Defense. **World Allergy Organ J**, v. 5, p. 9–19, 2012.

BJORKLUND, L. Acta orthopaedica scandinavica. **Supplementun**, v. 281, p. 67-80, 1998.

BLAIR, I. A. Endogenous glutathione adducts. **Curr drug metab**, v. 7, n. 8, p. 853-72, 2006.

BLANKENBERG, S. et al. Interleukin-18 and the risk of coronary heart disease in European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). **Circulation**, p. 2453–9, 2003.

BLUMBERG, J. B. et al. Impact of Cranberries on Gut Microbiota and Cardiometabolic Health: Proceedings of the Cranberry Health Research Conference 2015. **Adv Nutr An Int Rev J** [Internet], v. 7, n. 4, p. 759S–70S, 2016.

BOERS, M. et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. **Rheumatol Suppl**, v. 41, p. 86-9, 1994.

BOHNDORF, K.; SCHALM, J. Diagnostic radiography in rheumatoid arthritis: benefi ts and limitations. Baillieres **Clin Rheumatol**, v. 10, p. 399–407, 1996.

BORGES, P. K. de O. et al. Prevalence and characteristics associated with metabolic syndrome in Japanese-Brazilians with and without periodontal disease. **Cadernos de Saude Publica**, v. 23, n. 3, p. 657–68, mar. 2007.

BRENNAN, F. M.; MCINNES, I. B. Evidence that cytokines play a role in rheumatoid arthritis. **The Journal of Clinical Investigation**, v. 118, n. 11, p. 3537–45, nov. 2008.

BROWN, K. K. Rheumatoid lung disease. **Proc Am Thorac Soc**, v. 4, p. 443–8, 2007.

BURMESTER, G. R.; POPE, J. E. Novel treatment strategies in rheumatoid arthritis. **The Lancet**, v. 389, n. 10086, p. 2338–48, jun. 2017.

C¸ IMEN, M. Y. B. et al. Oxidant/antioxidant status of the erythrocytes from patients with rheumatoid arthritis. **Clin Rheum**, v. 19, 275–7, 2000.

CATRINA, A. I. et al. Mechanisms involved in triggering rheumatoid arthritis. **Immunological Reviews**, v. 269, n. 1, p. 162–74, jan. 2016.

CERIELLO, A.; QUATRARO, A.; GIUGLIANO, D. Diabetes mellitus and hypertension: the possible role of hyperglycaemia through oxidative stress. **Diabetologia**, v. 36, p. 265–6, 1993.

CIMEN, M. Y. B. et al. Oxidant/antioxidant status of the erythrocytes from patients with rheumatoid arthritis. **Clinical rheumatology**, v. 19, n. 4, p. 275-277, 2000.

CHAMBERS, B. K.; CAMIRE, M. E. Can cranberry supplementation benefit adults with type 2 diabetes? **Diabetes Care**, v. 26, p. 2695–6, 2003.

CHIMENTI, M. S. et al. The interplay between inflammation and metabolism in rheumatoid arthritis. **Cell death & disease**, v. 6, p. e1887, 2015.

CHOI, K. M. et al. Serum adiponectin, interleukin-10 levels and inflammatory markers in the metabolic syndrome. **Diabetes Res Clin Pract**, v. 75, p. 235–40, 2007.

CHUNG, C. P. et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. **Atherosclerosis**, v. 196, n. 2, p. 756–63, fev. 2008.

CROWSON, C. S. et al. Contribution of obesity to the rise in incidence of rheumatoid arthritis. **Arthritis Care and Research**, v. 65, n. 1, p. 71–7, 2013.

DA MOTA, L. M.; DOS SANTOS NETO, L. L.; DE CARVALHO, J. F. Autoantibodies and other serological markers in rheumatoid arthritis: predictors of disease activity? **Clin Rheumatol**, v. 28, n. 10, p. 1127-34, 2009.

DANDONA, P. et al. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. **Circulation**, v. 111, p. 1448–54, 2005.

DAS, U. N. Metabolic syndrome X: an inflammatory condition? **Curr Hypertens Rep**, v. 6, p. 66–73, 2004.

DESSÌ, A.; ATZEI, A.; FANOS, V. Cranberry in children: prevention of recurrent urinary tract infections and review of the literature. **Revista Brasileira de Farmacognosia**, v. 21, n. 5, p. 807–13, out. 2011.

DEVLIN, J. The acute phase and function in early rheumatoid arthritis. C-reactive protein levels correlate with functional outcome. **J Rheumatol**, v. 24, p. 9-13, 1997.

DOHADWALA, M. M. et al. Effects of cranberry juice consumption on vascular function in patients with coronary artery disease 1 – 3. **Am J Clin Nutr**, p. 934–40, 2011.

DOROFEJEVA, K. et al. Procedia Food Science Vitamin C content in Latvian cranberries dried in convective and microwave vacuum driers. **Procedia Food Sci** [Internet], v. 1, n. 0, p. 433–40, 2011.

DUFFEY, K. J.; SUTHERLAND, L. A. Adult consumers of cranberry juice cocktail have lower C-reactive protein levels compared with nonconsumers. **Nutrition Research**, v. 35, n. 2, p. 118–26, 2015.

DUTHIE, G. G. et al. Increased salicylate concentrations in urine of human volunteers after consumption of cranberry juice. **Journal of Agricultural and Food Chemistry**, v. 53, n. 8, p. 2897–900, 20 abr. 2005.

DUTHIE, S. J. et al. The effects of cranberry juice consumption on antioxidant status and biomarkers relating to heart disease and cancer in healthy human volunteers**. Eur J Nutr**, v. 45, p. 113–22, 2006.

ELLABBAN, A. et al. Impact of obesity on functional and laboratory parameters in patients with rheumatoid arthritis. **Egyptian Rheumatology and Rehabilitation**, v. 43, n. 1, p. 21, 2016.

ERLUND, I. et al. Favorable effects of berry consumption on platelet function, blood pressure, and HDL cholesterol. **Am J Clin Nutr**, v. 87, p. 323–31, 2008.

ESRA BIRBEN *et al.* Oxidative Stress and Antioxidant Defense. **World Allergy Organ J.** v. 5, n. 1, p. 9–19 , 2012.

FELSON, D. T. et al. The American College of Rheumatology preliminar core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. **Arthritis Rheum**, v. 36, p. 729-40, 1993.

FESTA, A. et al. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). **Circulation**, v. 102, p. 42–7, 2000.

FESTA, A. et al. The relation of body fat mass and distribution to markers of chronic inflammation. **Int J Obes Relat Metab Disord**, v. 25, p. 1407–15, 2001.

FORD, E. S. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. **Diabetes Care**, v. 28, n. 7, p. 1769–78, jul. 2005.

FORD, E. S.; GILES, W. H.; GIETZ, W. H. *Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey.* **JAMA***,* v. 287, p. 356–*9, 2002.*

FRANCO, R. et al. “Environmental toxicity, oxidative stress and apoptosis: menage a trois,” **Mutation Research**, v. 674, n. 1-2, p. 3–22, 2009.

GABRIEL, S. E. et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. **Arthritis Rheum**, v. 48, p. 54–8, 2003.

GAMBHIR, J. K.; LALI, P.; JAIN, A. K. Correlation between blood antioxidant levels and lipid peroxidation in rheumatoid arthritis. **Clin Biochem**, v. 30, p. 351–5, 1997.

GARROD, A. B. Treatise on Nature and Treatment of Gout and Rheumatic Gout. London: **Walton and Maberly**, 1859.

GIUGLIANO, D. Dietary antioxidants for cardiovascular disease prevention. **Nutr Metab Cardiovasc Dis**, v. 10, p. 38–44, 2000.

GIUGLIANO, D.; CERIELLO, A.; PAOLISSO, G. Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress? **Metabolism**, v. 44, p. 363–8, 1995.

GOELDNER, I. et al. Association of anticyclic citrullinated peptide antibodies with extra-articular manifestations, gender, and tabagism in rheumatoid arthritis patients from southern Brazil. **Clin Rheumatol**, v. 22, 2011.

GOLDSMITH, C. H. et al. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profi les. OMERACT Committee. **J Rheumatol**, v. 20, p. 561-5, 1993.

GONZALEZ FLECHA, B.; LLESUY, S.; BOVERIS, A. Hydroperoxide-initiated chemiluminescence: An assay for oxidative stress in biopsies of heart, liver, and muscle. **Free Radical Biology and Medicine**, v. 10, n. 2, p. 93–100, 1991.

GRUNDY, S. et al. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. **Circulation**, v. 106, n. 25, p. 3143–421, 2002.

GUAY, D. R. P. Cranberry and Urinary Tract Infections. **Drugs**, v. 69, n. 7, p. 775–807, maio 2009.

HALLIWELL, B. et al. The characterization of antioxidants. **Food Chem Toxicol**, v. 33, n. 7, p. 601-17, 1995.

HALLIWELL, B.; GUTTERIDGE, J. M. Free radicals, ageing, and disease. In Free Radicals in Biology and Medicine, **Clarendon Press**: **Oxford**, UK, 1996; 417–506, 1996.

HANLEY, A. J. G. et al. Prediction of type 2 diabetes mellitus with alternative definitions of the metabolic syndrome: The Insulin Resistance Atherosclerosis Study. **Circulation**, v. 112, n. 24, p. 3713–21, 2005.

HANSEL, B. et al. Metabolic syndrome is associated with elevated oxidative stress and dysfunctional dense high-density lipoprotein particles displaying impaired antioxidative activity. **J Clin Endocrinol Metab**, v. 89, p. 4963–71, 2004.

HANSON, R. L. et al. Components of the "metabolic syndrome" and incidence of type 2 diabetes. **Diabetes**, *v.* 51, p. 3120–*7, 2002.*

HEINRICH, P. C.; CASTELL, J. V.; ANDUS, T. Interleukin-6 and the acute phase response. **Biochem J**, v. 265, p. 621–36, 1990.

HITCHON, C. A.; EL-GABALAWY, H. S. Oxidation in rheumatoid arthritis. **Arthritis Research & Therapy**, v. 6, n. 6, p. 265–78, 2004.

HODJAT, M.; REZVANFAR, M. A.; ABDOLLAHI, M. "A systematic review on the role of environmental toxicants in stem cells aging". **Food and Chemical Toxicology,** v. 86, p. 298–308, 2015.

HU, M. L. Measurement of protein thiol groups and glutathione in plasma. **Methods Enzymol**, v. 233, p. 380–5, 1994.

ISOMAA, B. et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. **Diabetes Care**, v. 24, p. 683–*9,* 2001.

KALYANARAMAN, B. Teaching the basics of redox biology to medical and graduate students: Oxidants, antioxidants and disease mechanisms. **Redox Biology**, v. 1, n. 1, p. 244–57, 8 fev. 2013.

KEANEY, J. F. et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study **Arterioscler Thromb Vasc Biol**, v. 23, p. 434–9, 2003.

KEREKES, G. et al. Rheumatoid arthritis and metabolic syndrome. **Nature reviews. Rheumatology**, v. 10, n. 11, p. 691–6, nov. 2014.

KIM, M. J. et al. Effects of cranberry powder on serum lipid profiles and biomarkers of oxidative stress in rats fed an atherogenic diet. **Nutr Res Pract** [Internet], v. 2, n. 3, p. 158–64, 2008.

KOENIG, W. et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. **Circulation**, v. 99, p. 237–42, 1999.

L A COLEMAN, R. R. Arthritis. In: PRENTICE, B. C. L. A. A. (Editor). **Encyclopedia of Human Nutrition**. 2. ed. Oxford UK: Elsevier, p. 163-9, 2005.

LAAKSONEN, D. E. et al. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. **Am J Epidemiol**, v. 156, p. 1070–*7,* 2002*.*

LAKKA, H. M. et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. **JAMA**, v. 288, p. 2709–16, 2002.

LEE, I. T. et al. Effect of cranberry extracts on lipid profiles in subjects with Type 2 diabetes. **Diabet Med**, v. 25, p. 1473–7, 2008.

LIBBY, P.; RIDKER, P.M.; MASERI, A. Inflammation and atherosclerosis. **Circulation.** V. 105, n.9, p. 1135-1143, 2002.

LORENZO, C. et al. San Antonio Heart Study. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. **Diabetes Care**, v. 26, p. 3153–*9,* 2003.

LUC, G. et al. C-reactive protein, interleukin-6, and fibrinogen as predictors of coronary heart disease: the PRIME Study. **Arterioscler Thromb Vasc Biol**, v. 23, p. 1255–61, 2003.

MACHOLD, K. P. et al. Very recent onset arthritis – clinical, laboratory, and radiological fi ndings during the fi rst year of disease. **J Rheumatol**, v. 29, p. 2278–87, 2002.

MARCHAND, S. et al. Nutrient signature of Quebec (Canada) cranberry (Vaccinium macrocarpon Ait.). **Revista Brasileira de Fruticultura**, v. 35, n. 1, p. 292–304, mar. 2013.

MATSUZAWA, Y. et al. Adiponectin and Metabolic Syndrome. **Arterioscler Thromb Vasc Biol**, v. 24, p. 29–33, 2004.

MCKAY, D. L.; BLUMBERG, J. B. Cranberries (Vaccinium macrocarpon) and cardiovascular disease risk factors. **Nutr Rev**, v. 65, n. 11, p. 490–502, 2007.

MIESEL, R.; MURPHY, M. P.; KRÖGER, H. Enhanced Mitochondrial Radical Production in Patients with Rheumatoid Arthritis Correlates with Elevated Levels of Tumor Necrosis Factor alpha in Plasma. **Free Radical Research**, v. 25, n. 2, p. 161–9, 7 jan. 1996.

MILES, E. A.; CALDER, P. C. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. **Br J Nutr**, v. 107, n. 2, p. S171-84, 2012.

MINAUR, N. J. et al. Outcome after 40 years with rheumatoid arthritis: a prospective study of function, disease activity, and mortality. **J Rheumatol Suppl**, v. 69, p. 3–8, 2004.

MYASOEDOVA, E. et al. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955-2007. **Arthritis and Rheumatism**, v. 62, n. 6, p. 1576–1582, 2010.

MOTA, L. M. H. et al. Consenso da Sociedade Brasileira de Reumatologia 2011 para o diagnóstico e avaliação inicial da artrite reumatoide. **Revista Brasileira de Reumatologia**, v. 51, n. 3, p. 207-219, jun. 2011.

NAKAJIMA, A. Cardiovascular diseases in rheumatoid arthritis. Nihon rinsho. Japanese **Journal of Clinical Medicine**, v. 74, n. 6, p. 1012–6, jun. 2016.

NAVARRO-GONZÁLVEZ, J. A.; GARCÍA-BENAYAS, C.; ARENAS, J. Semiautomated measurement of nitrate in biological fluids. **Clinical Chemistry**, v. 44, n. 3, p. 679–81, mar. 1998.

NETO, C. C. Cranberry and blueberry: evidence for protective effects against cancer and vascular diseases. **Mol Nutr Food Res**, v. 51, p. 652–64, 2007.

NOVOTNY, J. A. et al. Cranberry juice consumption lowers markers of cardiometabolic risk, including blood pressure and circulating C-reactive protein, triglyceride, and glucose concentrations in adults. **The Journal of Nutrition**, v. 145, n. 6, p. 1185–93, jun. 2015.

O¨ ZGU¨NES, H.; GU¨RER, H.; TUNCER, S. Correlation between plasma malondialdehyde and ceruloplasmin activity values in rhematoid arthritis. **Clin Biochem**, v. 28, p. 193–4, 1995.

OKTYABRSKY, O. N.; SMIRNOVA, G. V. Redox regulation of cellular functions. **Biochemistry** (Mosc), v. 72, n. 2, p. 132-45, 2007.

OSTRAKHOVITCH, E. A.; AFANASEV, I. B. Oxidative stress in rheumatoid arthritis leukocytes: suppression by routine and othe antioxidants and chelators. **Biochem Pharmacol**, v. 62, p. 743–6, 2001.

PATTISON, D. J.; HARRISON, R. A.; SYMMONS, D. P. M. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. **J Rheumatol**, v. 31, n. 7, p. 1310-9, 2004.

PEDERSEN, C. B. et al. Effects of blueberry and cranberry juice consumption on the plasma antioxidant capacity of healthy female volunteers. **Eur J Clin Nutr**, v. 54, p. 405–8, 2000.

PENCKOFER, S.; SCHWERTZ, D.; FLORCZAK, K. Oxidative stress cardiovascular disease in type 2 diabetes: the role of antioxidants and pro-oxidants. **J Cardiovasc Nurs** 16: 68–85, 2002.

PICERNO, V. et al. One year in review: the pathogenesis of rheumatoid arthritis. **Clinical and Experimental Rheumatology**, v. 33, n. 4, p. 551–8, 2015.

PLANT, M. J. et al. Patterns of radiological progression in early rheumatoid arthritis: results of an 8 year prospective study. **J Rheumatol**, v. 25, p. 417–26, 1998.

PREVOO, M. L. et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. **Arthritis and rheumatism**, v. 38, n. 1, p. 44–8, jan. 1995

QIN, B. et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. **Arthritis Research & Therapy**, v. 17, n. 1, p. 86, 2015.

REAVEN, G. M. Role of insulin resistance in human disease (syndrome X): an expanded definition. **Annu Rev Med**, v. 44, p. 121–31, 1993.

RENNIE, K. L. et al. Nutritional management of rheumatoid arthritis: a review of the evidence. **J Hum Nutr Diet**, v. 16, n. 2, p. 97-109, 2003.

REPETTO, M. et al. Oxidative stress in blood of HIV infected patients. **Clinica Chimica Acta**, v. 255, n. 2, p. 107–17, 1996.

RESNICK, H. E. et al. Strong Heart Study. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: the Strong Heart Study. **Diabetes Care**, v. 26, p. 861–*7, 2003.*

REUTER, S. et al. Oxidative stress, inflammation, and cancer: How are they linked? **Free Radic Biol Med** [Internet], v. 49, n. 11, p. 1603-16, 2010. Disponível em: <http://dx.doi.org/10.1016/j.freeradbiomed.2010.09.006>. Acesso em: 11 jan. 2018.

REZNICK, A. Z.; PACKER, L. Oxidative damage to proteins: Spectrophotometric method for carbonyl assay. In: **Methods in Enzymology**, v. 233, p. 357–63, 1994.

RICCIONI, G. et al. Antioxidant vitamin supplementation in cardiovascular diseases. **Ann Clin Lab Sci**, v. 37, n. 1, p. 89-95, 2007.

RIDKER, P. M. et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. **Circulation**, v. 101, p. 1767–72, 2000.

RIDKER, P. M. et al. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. **Circulation**, p. 1962–7, 1998.

RITCHIE, D. M. et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. **Q J Med**, v. 37, p. 393-406, 1968.

RUEL, G. et al. Changes in plasma antioxidant capacity and oxidized low-density lipoprotein levels in men after short-term cranberry juice consumption. **Metabolism**, v. 54, p. 856–61, 2005.

RUEL, G. et al. Favourable impact of low-calorie cranberry juice consumption on plasma HDL-cholesterol concentrations in men. **Br J Nutr**, v. 96, n. 2, p. 357–64, 2006.

Ruel G, Couillard C. Evidences of the cardioprotective potential of fruits: the case of cranberries. **Mol Nutr Food Res**, v. 51, p.692–701, 2007.

RUEL, G. et al. Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men. **Br J Nutr**, v. 99, n. 2, p. 352–9, 2008.

RUEL, G. et al. Plasma matrix metalloproteinase (MMP)-9 levels are reduced following low-calorie cranberry juice supplementation in men. **J Am Coll Nutr**, [Internet], v. 28, n. 6, p. 694–701, 2009.

SCHULZ, K. F.; GRIMES, D. A. Multiplicity in randomized trials I: endpoints and treatments. **Lancet**, 2005; v. 365, p. 1591-5, 2005.

SCOTT, D. L. et al. Disease activity in rheumatoid arthritis: preliminary report of the Consensus Study Group of the European Workshop for Rheumatology Research. **Clin Exp Rheumatol**, v. 10, p. 521-5, 1992.

SCRIVO, R. et al. Rheumatic diseases and obesity: Adipocytokines as potential comorbidity biomarkers for cardiovascular diseases. **Mediators of Inflammation**, v. 2013, p. 1–14, 2013.

SIEGEL, J. N.; ZHEN, B. G. Use of the American College of Rheumatology N (ACR-N) index of improvement in rheumatoid arthritis: argument in favor. **Arthritis Rheum**, 2005; v. 52, p. 1637-41, 2005.

SIES, H. Oxidative stress: introductory remarks. In: _. **Oxidative Stress. Academic Press**. London: 1985. p. 1-507.

SIMÃO, T. N. C. et al. Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome. **Br J Nutr** [Internet], v. 100, n. 10, p. 1885–94, 2013.

SKEOCH, S.; BRUCE, I. N. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nature Reviews. **Rheumatology,** v. 11, n. 7, p. 390–400, jul. 2015.

SMOLEN, J. S. et al. A simplifi ed disease activity index for rheumatoid arthritis for use in clinical practice. **Rheumatology**, v. 42, p. 244-57, 2003.

SMOLEN, J. S.; ALETAHA, D.; MCINNES, I. B. Rheumatoid arthritis. **Lancet** (London, England), v. 388, n. 10055, p. 2023–38, 22 out. 2016.

SONEJA, A.; DREWS, M.; MALINSKI, T. Role of Nitric oxide, nitroxidative ad oxidative stress in wound healing. **Pharmacol Rep**, v. 57, p. 108-19, 2005.

SPECTOR, T. D. Rheumatoid arthritis. **Rheum Dis Clin North Am**, v. 16, p. 513–37, 1990.

STOCKER, R.; KEANEY, J. F. Role of oxidative modification in atherosclerosis. **Physiol**, v. 84, p. 1381–1478, 2004.

SURH, Y. J. et al. Redox-sensitive transcription factors as prime targets for chemoprevention with anti-inflammatory and antioxidative phytochemicals**. J Nutr**, v. 135, n. 12, p. 2993-3001, 2005.

SURH, Y. J. **Oxidative stress, inflammation, and healt.** Packer L (ed). Londres: Taylor & Francis, 2005.

TIPTON, D. A.; CHRISTIAN, J.; BLUMER, A. Effects of cranberry components on IL-1β-stimulated production of IL-6, IL-8 and VEGF by human TMJ synovial fibroblasts. **Archives of Oral Biology**, v. 68, p. 88–96, ago. 2016.

TOSHIMA, Shun-ichi et al. Circulating oxidized low density lipoprotein levels: a biochemical risk marker for coronary heart disease. **Arteriosclerosis, thrombosis, and vascular biology**, v. 20, n. 10, p. 2243-2247, 2000.

TUGWELL, P.; BOMBARDIER, C. A methodologic framework for developing and selecting endpoints in clinical trials**. J Rheumatol**, v. 9, p. 758-62, 1982.

TURESSON, C. et al. Incidence and predictors of severe extra-articular disease manifestations in an early rheumatoid arthritis inception cohort. **Ann Rheum Dis**, v. 66, n. 11, p. 1543-44, 2007.

VALKO, Marian et al. Free radicals and antioxidants in normal physiological functions and human disease. **The international journal of biochemistry & cell biology**, v. 39, n. 1, p. 44-84, 2007.

VAN DER HEIJDE, D. M. et al. Development of a disease activity score based on judgment in clinical practice by rheumatologists. **J Rheumatol**, v. 20, p. 579-81, 1993.

VAN DER HEIJDE, D. M. et al. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. **Ann Rheum Dis**, v. 51, p. 177-81, 1992.

VAN DER HEIJDE, D. M. Joint erosions and patients with early rheumatoid arthritis. **Br J Rheumatol**, v. 34, n. 2, p. 74–8, 1995.

VAN GESTEL, A. M. et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. **Arthritis Rheum**, v. 39, p. 34-40, 1996.

VAN GESTEL, A. M.; HAAGSMA, C. J.; VAN RIEL, P. L. Validation of rheumatoid arthritis improvement criteria that include simplifi ed joint counts. **Arthritis Rheum**, v. 41, p. 1845-50, 1998.

VASCONCELOS, S. M. L. et al. Reactive oxygen and nitrogen species, antioxidants and markers of oxidative damage in human blood: main analytical methods for their determination. **Quim**, v. 30, p. 1323–38, nov. 2007.

VATTEM, D. A.; GHAEDIAN, R.; SHETTY, K. Enhancing health benefits of berries through phenolic antioxidant enrichment: focus on cranberry. **Asia Pac J Clin Nutr**, v. 14, p. 120–30, 2005.

VINSON, J. A. et al. Cranberries and cranberry products: powerful in vitro, ex vivo, and in vivo sources of antioxidants. **J Agric Food Chem**, v. 56, p. 5884–91, 2008.

VISSER, H. Early diagnosis of rheumatoid arthritis. **Best Pract & Res Clin Rheum**, v. 19, p. 55-72, 2005.

WALLENFELDT, K. et al. Oxidized low-density lipoprotein in plasma is a prognostic marker of subclinical atherosclerosis development in clinically healthy men. **J Intern Med**, v. 256, p. 413–20, 2004.

WANG, G. et al. Markers of oxidative and nitrosative stress in systemic lupus erythematosus: Correlation with disease activity. **Arthritis Rheum**, v. 62, p. 2064–72, 2010.

WANG, Y. et al. An LC-MS Method for Analyzing Total Resveratrol in Grape Juice ,

Cranberry Juice , and in Wine An LC-MS Method for Analyzing Total Resveratrol in Grape Juice , Cranberry Juice , and in Wine. **Jounal Agric food Chem**, v. 50, n. 3, p. 431–5, 2002.

WEST, I. C. Radicals and oxidative stress in diabetes. **Diabetic Med**, v. 17, p. 171–80, 2000.

WING, D. A. et al. Daily Cranberry Juice for the Prevention of Asymptomatic Bacteriuria in Pregnancy: A Randomized, Controlled Pilot Study. **J Urol**, v. 180, n. 4, p. 1367–72, 2008.

WITKO-SARSAT, V. et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. **Journal of immunology (Baltimore, Md. : 1950)**, v. 161, n. 5, p. 2524–32, set. 1998.

WOLFE, F.; SHARP, J. T. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. **Arthritis Rheum**, v. 41, p. 1571–82, 1998.

WOOLF, A. D. How to assess musculoskeletal conditions. History and physical examination. **Best Pract Res Clin Rheumatol**, v. 17, n. 3, p. 381-402, 2003.

WOOLF, A. D.; KESSON, K. Editorial. Understanding the burden of musculoskeletal conditions. **British Medical Journal**, v. 322, p. 1079–80, 2001.

YOKOZAWA, T. et al. Antioxidative activity of green tea treated with radical initiator 2, 2'-azobis(2-amidinopropane) dihydrochloride. **Journal of Agricultural and Food Chemistry**, v. 48, n. 10, p. 5068–73, 2000.

APÊNDICE A - FICHA DE AVALIAÇÃO

FICHA DE AVALIAÇÃO DOS PACIENTES COM ARTRITE REUMATÓIDE

NOME: _____FONE:_____
Endereço:_____
RG: _____
IDADE ou DN: _____
SEXO: feminino ( ) masculino ( )

AVALIAÇÃO TEMPO (____)

TEMPO DE DIAGNÓSTICO: _____

DAS 28: _____

COMPROMETIMENTO SISTEMICO EXTRA-ARTICULAR:
pulmonar ( ), vasculite ( ), ocular ( ), nodulos reumatoides ( ), cardíaco ( ), SNC ( )

OUTRAS DOENÇAS:
HAS ( ), DM ( ), dislipidemia ( ), IAM ( ), AVC ( ), outros: _____
outra colagenose ( ): _____

MEDICAÇÕES
( ) Prednisona dose: _____
( ) Metotrexate dose: _____
( ) Hidroxicloroquina/Cloroquina dose: _____
( ) Sulfassalazina dose: _____
( ) Leflunomide dose: _____
( ) Etanercepte dose: _____
( ) Adalimumabe dose: _____
( ) Infliximabe dose: _____
( ) Tocilizumabe dose: _____
( ) Abatacepte dose: _____
( ) Rituximabe dose: _____
( ) Ciclofosfamida dose: _____
( ) outros:
_____

TABAGISMO: sim ( ) não ( )

ATIVIDADE FISICA: sim ( ) não ( )
tipo: _____ frequência: _____ há quanto tempo: _____

DADOS ANTROPOMÉTRICOS

Altura (cm)	Peso (kg)	IMC (kg/m2)	Circunferência Abdominal (cm)	Pressão Arterial (mm/Hg)

APÊNDICE B - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Termo de Consentimento Livre e Esclarecido

Título da pesquisa: “Influência da ingestão de suco de Cranberry de baixa caloria sobre o metabolismo, processo inflamatório e o estresse oxidativo em pacientes com artrite reumatoide”

Prezado (a) Senhor (a):

Gostaríamos de convidá-lo (a) a participar da pesquisa “Influência da ingestão de suco de Cranberry de baixa caloria sobre o processo inflamatório e o estresse oxidativo em pacientes com artrite reumatoide”, realizada no Hospital Universitário de Londrina. O objetivo dessa pesquisa é avaliar se o consumo de suco de Cranberry, podem melhorar a inflamação e o estresse oxidativo decorrentes da artrite reumatoide, bem como reduzir a atividade da doença. A sua participação é muito importante e ela se daria da seguinte forma: em um primeiro momento, como de rotina, você passará por uma avaliação clínica ambulatorial pelo médico reumatologista e uma coleta de sangue para análises laboratoriais. A partir desse momento, de acordo com um sorteio, você será incluído em um de 1 grupo: (1) suco de Cranberry (90 dias) (dieta habitual por 90 dias). Após esse período você retornará ao ambulatório para que as avaliações descritas acima sejam repetidas e possamos verificar os efeitos destas intervenções. Gostaríamos de esclarecer que sua participação é totalmente voluntária, podendo você: recusar-se a participar, ou mesmo desistir a qualquer momento sem que isto acarrete qualquer ônus ou prejuízo à sua pessoa. Informamos ainda que as informações serão utilizadas somente para os fins desta pesquisa e serão tratadas com o mais absoluto sigilo e confidencialidade, de modo a preservar a sua identidade.

O consumo de suco de Cranberry não causam riscos à saúde das pessoas. Os benefícios esperados são redução da inflamação, do estresse oxidativo e de fatores que possam favorecer o desenvolvimento de doenças do coração. Além disso, espera-se também que ocorra uma melhora dos sintomas da doença como dores, inchaço, rigidez nas articulações e na sua qualidade de vida.

Informamos que o (a) senhor (a) não pagará nem será remunerado por sua participação.

Caso você tenha dúvidas ou necessite de maiores esclarecimentos pode nos contatar Nataly S. B. Thimoteo (Telefone: 18-981015484; e-mail: naty_bandiera@hotmail.com) ou procurar o Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Estadual de Londrina, na Avenida Robert Kock, nº 60, ou no telefone 33712490. Este termo deverá ser preenchido em duas vias de igual teor, sendo uma delas, devidamente preenchida e assinada entregue a você.

Londrina, ___ de _____de 201_____.

Pesquisador Responsável: Prof. Dr Isaias Dichi. RG: 9.922.731-1

_____, tendo sido devidamente esclarecido sobre os procedimentos da pesquisa, concordo em participar voluntariamente da pesquisa descrita acima.

Assinatura (ou impressão dactiloscópica):_____

Data:_____

Obs: Caso o participante da pesquisa seja menor de idade, deve ser incluído o campo para assinatura do menor e do responsável.

ANEXO A – PARECER CONSUBSTANCIADO DO COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS DA UNIVERSIDADE ESTADUAL DE LONDRINA

UNIVERSIDADE ESTADUAL DE LONDRINA - UEL/ HOSPITAL REGIONAL DO NORTE DO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Influência da ingestão de óleo de peixe e suco de cranberry de baixa caloria sobre o processo inflamatório e o estresse oxidativo em pacientes com artrite reumatoide

Pesquisador: Isaias Dichi
Área Temática:
Versão: 4
CAAE: 13426014.6.0000.5231
Instituição Proponente: CCS - Departamento de Clínica Médica
Patrocinador Principal: MINISTERIO DA CIENCIA, TECNOLOGIA E INOVACAO

DADOS DO PARECER

Número do Parecer: 617.289
Data da Relatoria: 14/04/2014

Apresentação do Projeto:
Trata-se da resposta a uma pendência indicada no parecer 575.753.

Objetivo da Pesquisa:
Idem ao parecer 575.753.

Avaliação dos Riscos e Benefícios:
Idem ao parecer 575.753.

Comentários e Considerações sobre a Pesquisa:
Idem ao parecer 575.753.

Considerações sobre os Termos de apresentação obrigatória:
Idem ao parecer 575.753.

Recomendações:
Não há.

Conclusões ou Pendências e Lista de Inadequações:
Não há.

Endereço: AVENIDA ROBERT KOCH, 60
Bairro: VILA OPERÁRIA **CEP:** 86.038-440
UF: PR **Município:** LONDRINA
Telefone: (43)3371-2490 **E-mail:** cep268@uel.br

UNIVERSIDADE ESTADUAL DE LONDRINA - UEL/ HOSPITAL REGIONAL DO NORTE DO

Continuação do Parecer: 617.289

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Parecer referendado.

LONDRINA, 15 de Abril de 2014

Assinador por:
Paula Mariza Zedu Alliprandini
(Coordenador)

Endereço: AVENIDA ROBERT KOCH, 60
Bairro: VILA OPERÁRIA **CEP:** 86.038-440
UF: PR **Município:** LONDRINA
Telefone: (43)3371-2490 **E-mail:** cep268@uel.br

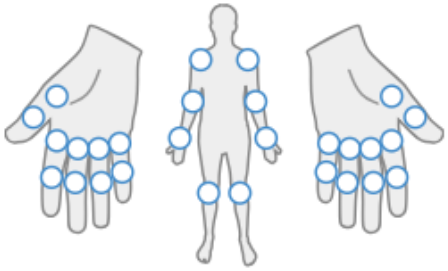
ANEXO B: CALCULADORA DE ÍNDICE DE ATIVIDADE DA DOENÇA-DAS 28

Joint score

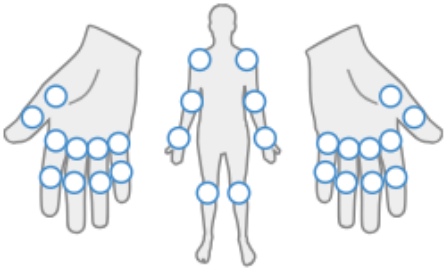
Type score

Choose from diagram

Tender joints



Swollen joints



Measures

Patient global assessment of disease activity (0-10)	0
Care provider global assessment of disease activity (0-10)	0

Record date

Recorded on	14/06/2018

Score 0.00 *Remission*

Record this score

Reset