1 **Effect of a tart cherry juice supplement on arterial stiffness and inflammation in**

2 **healthy adults: a randomised controlled trial.**

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17

18 **Abstract**

19 Tart cherries are a particularly rich source of anthocyanins. Evidence indicates that dietary

20 intake of anthocyanins is inversely associated with arterial stiffness. We conducted an open-

21 label randomised placebo controlled study to determine whether a tart cherry juice

22 concentrate (Cherry Active®) reduced arterial stiffness, inflammation and risk markers for

23 cardiovascular disease in 47 healthy adults (30 – 50 y). Participants consumed 30 ml of

24 cherry concentrate diluted to a volume of 250 ml with water or the same volume of an energy

25 matched control drink daily for 6 weeks. Measurements were taken at baseline and at the end

26 of the intervention. There was no effect of the intervention on arterial stiffness (P=0.218), c-

27 reactive protein (*P*=0.220), systolic blood pressure (*P*=0.163), diastolic blood pressure

28 (*P*=0.121), total cholesterol (*P*=0.342) and high density lipoprotein cholesterol (*P*=0.127). At

29 the end of the intervention, plasma antioxidant capacity (measured as the ferric reducing

30 ability of plasma (FRAP) was significantly higher in the intervention group than the control

31 group (*P*=0.012). We conclude that a tart cherry juice concentrate rich in anthocyanins has no

32 effect on arterial stiffness, c-reactive protein and risk markers for cardiovascular disease, but

33 evokes a minor increase in antioxidant status in healthy adults.

34

35 **Introduction**

36 Epidemiological studies indicate that the consumption of foods rich in flavonoids reduces the

37 risk of cardiovascular disease, with some evidence that anthocyanins may be particularly

38 protective [1-3]. Cherries are a rich source of flavonoids, especially anthocyanins [4-5]. In

39 cell culture and animal models, cherry extracts or isolated anthocyanins have been shown to

40 exert a range of potentially cardioprotective effects including, increasing nitric oxide

41 production and antioxidant status, reducing lipid oxidation and inhibiting inflammation [6-9].

42 Anti-inflammatory effects have also been reported in a limited number of human studies [10-

43 13]. In healthy middle-aged adults, the daily consumption of sweet cherries for 4 weeks

44 reduced several markers of inflammation [10, 11]. Also, supplementation with tart cherry

45 juice reduced exercise-induced inflammation in marathon runners and in adults completing a

46 resistance exercise task [12, 13].

47 There is interest in whether diets rich in dietary anthocyanins can reduce arterial stiffness

48 and therefore risk of cardiovascular disease [14]. Arterial stiffness is determined by the

49 structural properties of the arterial wall, blood pressure and endothelial function [15]. Some

50 experimental evidence indicates that anthocyanins can improve endothelial function via

51 induction of endothelial nitric oxide synthase, so by extrapolation anthocyanins may reduce

arterial stiffness [16, 17]. In patients with hypercholestrolaemia, endothelial function was improved by a single dose of anthocyanins (320 mg) and a period of chronic supplementation (320 mg/d x 12 weeks) [17]. In the chronic supplementation study, endothelial function was improved > 12 hours after consumption of the last dose of anthocyanins when intact anthocyanins and their metabolites could not be detected in the plasma of participants. The authors speculated that anthocyanins may have accumulated in tissues [17].

In a cross-sectional study of women from the TwinsUK registry, arterial stiffness was inversely associated with anthocyanin intake, but not with total flavonoid intake [14]. The risk of residual confounding means that casual inference cannot be ascertained from cross-sectional studies, so intervention studies are needed to demonstrate that anthocyanin rich foods can reduce arterial stiffness [14]. In a recent study, daily supplementation with cranberry juice (rich in anthocyanins; 94 mg/d) for 4 weeks reduced arterial stiffness in overweight adults with coronary artery disease [18]. The effect of anthocyanin rich foods on arterial stiffness in healthy adults remains largely unexplored. In the present study we aimed to determine whether a commercial tart cherry juice concentrate rich in anthocyanins reduced arterial stiffness, inflammation and other markers of cardiovascular risk in healthy adults.

METHODS

Participants A total of 47 (29 female and 18 male) apparently healthy, non-smoking volunteers (age 30-50 y) were recruited through University email distribution lists, posters and personal contacts. Exclusion criteria included taking medication for heart disease, hypertension or diabetes, regular consumption of cherries or cherry juice and the use of antioxidant supplements. The study was approved by Sheffield Hallam University Ethics Committee and all volunteers gave written informed consent. The study was conducted between May 2010 and August 2011.

Study design. The study was a 6-week parallel open-label intervention of a daily supplement of cherry juice concentrate (30 ml diluted with 220 ml of water; Cherry Active®) *versus* a control drink of lemonade (250 ml/d; Sprite®). Both drinks were delivered to participants at the start of the intervention; those consuming the cherry juice were instructed to store the juice in their refrigerators before consumption. The concentrated cherry juice was dispensed automatically using a pump-action dispenser from a 950 ml bottle, whilst the lemonade was supplied in individual 250 ml bottles. Participants consumed the drinks during the day, according to their preference.

Participants were stratified by gender and age (30-39 years and > 40 years) and then block randomised to treatment by an investigator who was not involved in recruitment. Concealed envelopes were used to inform the researchers responsible for recruitment of the treatment allocation; this information was not made available until after baseline measurements were completed. Compliance to the intervention was recorded through participants keeping a daily tick-sheet of drinks consumed. It was emphasised to all participants that they should adhere to their usual diet and maintain usual exercise patterns in conjunction with daily consumption of the test drinks.

Our primary outcome variable was change in pulse wave velocity (PWV); our secondary outcome variable was change in c-reactive protein (CRP). Power calculations were based on a 10% change in PWV. A sample size of 50 (25 per arm) was calculated to detect a 10% change in PWV with 80% power and an alpha value of 0.05, using variance estimates of PWV (SD = 1.06, n=57) from a study of PWV (unpublished data).

Tart cherry juice concentrate and placebo beverage

The tart cherry juice concentrate was supplied by Cherry Active, Sunbury UK. A 30 ml serving of tart cherry juice was diluted with 220 ml of water prior to consumption. Each serving was estimated to contain the equivalent of 90-100 Montmorency tart cherries. The

composition of the juice was analysed by an independent laboratory (Atlas Bioscience Inc, Tuscan, AZ, USA). Each 30 ml serving of the concentrate contained 102 kcal, 24.5 g carbohydrate, 1.1 g protein, trace amounts of fat, 2.6 g fibre, 9.72 mg ascorbic acid, 408 µg β-carotene and trace amounts of sodium. The total anthocyanin content per serving was 273.5 mg. The predominant anthocyanins normally present in tart cherries are cyanidin derivatives with smaller amounts of peonidin-3-rutinoside. Other compounds typically present include hydroxycinnamic acids, flavonols and the indoleamine, melatonin [4, 19, 20]. The very distinctive taste of the cherry concentrate made it difficult to blind the study. The placebo beverage (Sprite®, The Coca-Cola Company) was chosen because it closely matched the energy and macronutrient composition of cherry juice (109 kcal, 26.4 g CHO, 0 g fat, 0.1 g sodium per 250 ml) and was devoid of plant compounds, antioxidants and vitamins.

Measurements Participants attended Sheffield Hallam University on two occasions for vascular measurements, anthropometric measurements and blood sampling. All these were taken in the early morning after an overnight fast. On both occasions, PWV, systolic blood pressure (SBP), diastolic blood pressure (DBP) and body weight were measured and a blood sample was taken. Height was also measured at the baseline visit. Measurements were taken after a 15 min rest in the supine position to allow time for BP, cardiac function and vasomotor tone to reach resting levels.

Brachial-knee PWV was measured in the supine position using a Nicolet Vasoguard Microlight system (VIASYS Healthcare, USA) as previously described [21]. BP and heart rate were measured in triplicate at 2.5 min intervals in the supine position using a semi-automated Accutorr Plus™ sphygmomanometer (Datascope®, USA). The first reading was disregarded to prevent readings being affected by the defence mechanism (the rise in BP associated with anxiety of measurement, that tends to subside with subsequent measurements) [22] and mean SBP, DBP and heart rate were calculated from the second and

127 third measurements. The Accutorr Plus™ sphygmomanometer was calibrated prior to the

128 start of the study. The device meets the US Association for the Advancement of Medical

129 Instrumentation and British Hypertension Society criteria for accuracy and has been

130 recommended by the European Society of Hypertension [23].

131   Weight was measured to the nearest 0.1 kg using a SECA 709 mechanical column

132 scale and height was measured to the nearest 0.1 cm with a SECA 220 telescopic measuring

133 rod (SECA, Birmingham, UK).

134   Fasting capillary blood samples were collected for the determination of total

135 cholesterol, high density lipoprotein (HDL) cholesterol, CRP and total antioxidant activity

136 (ferric reducing ability of plasma; FRAP). Lipid variables were measured on a Reflotron Plus

137 reflectance photometer (Roche Diagnostics Ltd, Burgess Hill, UK). For the analysis of total

138 cholesterol a 30 µl sample of whole blood was collected into a capillary pipette and applied

139 to a Reflotron reagent strip (Inverness Medical, Stockport, UK). The within day precision

140 was 0.8% and the between day precision was 1.2%. For the determination of HDL, a 60 µl

141 sample of whole blood was collected into an EDTA-potassium coated microcentrifuge tube

142 (Sarstedt Ltd, Leicester, UK) and spun at 2000 g x 5 min. Plasma was then extracted and

143 applied to a Reflotron HDL cholesterol strip (Inverness Medical, Stockport, UK) for

144 immediate analysis. The within day precision was 7.0% and between day precision was 8.3%.

145 A 250 µl whole blood sample was also collected into a lithium-heparin coated

146 microcentrifuge tube (Sarstedt Ltd, Leicester, UK) and spun at 2000 **g** for 10 min at $4^{o}C$ to

147 extract plasma. The plasma was divided into two aliquots. One aliquot was stored at $-80^{o}C$

148 for the later analysis of CRP and the second aliquot was used for the immediate

149 determination of plasma antioxidant activity (FRAP). FRAP was measured as described by

150 Benzie and Strain [24] on a Cecil Series 1000 UV/Vis spectrophotometer (Cecile Instruments

151 Ltd, Cambridge, UK). The intra-assay coefficient of variation (CV) was 1.4% and the inter-

152 assay CV was 4.2%. Plasma CRP was measured using a commercially available ELISA kit

153 (MP Biomedicals UK, Cambridge, UK). The intra-assay CV was 11.5% and the inter-assay

154 CV was 12.3%.

155 *Statistical analysis* For each variable, analysis was restricted to participants for whom

156 baseline and end of study data were available (see Table 2 for *n* values). The effect of

157 treatment on post-intervention measures was analysed by a one way ANCOVA, with

158 adjustment for baseline [25]. The residuals from the model were tested for normality using

159 the Shapiro-Wilk test and log transformation was used when there was deviation from

160 normality. The criterion for significance was a $P<0.05$. All analyses were conducted using

161 SPSS version 20.0 (SPSS UK Ltd. Woking, UK).

162

163 **Results**

164 *Baseline characteristics, retention and compliance* Anthropometric, biochemical and

165 vascular measures were similar in randomisation groups at baseline (Table 1 & 2) and the

166 groups were balanced for sex and age. One participant withdrew from the study because they

167 did not like the taste of the cherry juice; all other participants completed the intervention

168 without report of adverse effects. Compliance to the intervention was good with 97% of

169 drinks consumed by the cherry juice group and 98% of drinks consumed by the placebo

170 group.

171 *Effect of intervention* There was no significant difference between the groups for the

172 primary outcome variable of PWV (Table 2). Cherry juice did not have any effect on CRP,

173 SBP, DBP, total cholesterol or HDL cholesterol relative to the placebo drink (Table 2).

174 Antioxidant status was significantly elevated at the end of the intervention in the cherry juice

175 group compared to the placebo group ($P=0.012$). In comparison to the cherry juice group

176   there was a weak trend towards an increase in bodyweight in the placebo group (adjusted

177   mean difference 0.69 (95% CI -0.07, 1.15) kg; *P*=0.073).

178

179   **Discussion**

180   There is some evidence from dietary observational studies that anthocyanin intake is

181   associated with PWV – a large study of 1872 women from the TwinsUK registry reported

182   that women with a high intake of dietary anthocyanins had lower PWV [14]. The present

183   study was designed to test the hypothesis that short-term dietary intervention with

184   anthocyanins supplied as tart cherry juice would reduce PWV and a range of other risk

185   markers for CVD in healthy adults. To our knowledge no other study has investigated the

186   effect of tart cherry juice on PWV. However, Dohadwala et al. [18] reported that a 4-week

187   intervention with double strength cranberry juice (supplying 94 mg/d of anthocyanins)

188   reduced carotid-femoral PWV (by approximately 0.5 m/s) in overweight adults with coronary

189   artery disease. Despite providing approximately 3 times the quantity of anthocyanins to our

190   participants we failed to observe a reduction in PWV. Differences in study design may

191   explain this discrepancy. Dohadwala et al. [18] studied a group of overweight adults with

192   elevated risk markers for cardiovascular disease, whereas our volunteers had a normal body

193   mass index (BMI) (approx. 24 kg/m^2) and were seemingly healthy. It is possible that in

194   healthy individuals, arterial stiffness is less responsive to a short-term increase in the intake

195   of anthocyanins. Moreover we measured brachial-knee PWV, which because it includes

196   segments of peripheral muscular arteries may be less amenable to dietary intervention than

197   carotid-femoral PWV. It is also possible that constituents of cranberry juice other than

198   anthocyanins may have driven the reduction in PWV observed by Dohadwala et al. [18].

199   The influence of supplementation with drinks rich in other polyphenolic compounds such as

200   green tea (rich in flavanols) [26] and pomegranate juice (rich in elagitannins but also a source

of anthocyanins) have also shown no effect on arterial stiffness [21], whilst supplementation with isolated clover isoflavone over a 6-week period lowered PWV in postmenopausal women and older men [27].

Cherry juice appeared to have no influence on BP in our sample of apparently healthy middle-aged men and women. There are no directly comparable studies, and those testing purified anthocyanins and extracts/juices rich in anthocyanins are inconsistent. A 4-wk intervention with a twice-daily supplement of 320 mg of purified anthocyanins failed to alter BP in middle-aged men with raised baseline BP [28]. Similarly, in elderly women supplementation with an elderberry extract (500 mg/d of anthocyanins) for 12 weeks failed to alter BP [29]. However, Chong et al [30] suggested that chokeberries may have hypotensive effects based on a single intervention study in patients with cardiovascular disease.

We also observed no change in CRP as a result of cherry juice supplementation. CRP is a recognised biomarker of systemic inflammation and a risk marker for cardiovascular events [31]. This lack of effect on CRP contrasts with the studies of Kelley et al. [10, 11] who reported that 280 g/d of sweet cherries (supplying approx. 100 mg/d anthocyanins) reduced CRP by 8% after 2 weeks of supplementation and by 25% after four weeks of supplementation. Although these changes in CRP seem to indicate that sweet cherries elicit a reduction in inflammation, the study lacked a control group so interpretation must be cautious. Our results also contrast with studies demonstrating that tart cherry juice attenuates the inflammatory response to marathon running and resistance exercise [12, 13]. This discrepancy may be explained by differences in dosing schedule (1 serving/d v 2 servings/d) or indicate that in healthy adults, tart cherry juice attenuates the response to an inflammatory challenge, but does not modulate baseline levels of inflammation.

Cherry juice has potent antioxidant effects [4, 32]. At the end of the current intervention, plasma antioxidant status (measured by the FRAP assay) was modestly elevated

226 in the tart cherry group in comparison to the control group, however, this was largely driven

227 by a fall in antioxidant status in the control group. This may reflect the displacement of

228 antioxidant containing beverages by the placebo drink. The FRAP assay probably has limited

229 sensitivity to detect an increase in antioxidant status in response to the tart cherry juice. The

230 main determinants of plasma FRAP are uric acid, which may be lowered by cherries and

231 ascorbate which is only present in low amounts in tart cherry juice [24, 33]. The contribution

232 of polyphenols to plasma FRAP activity is likely to be low [24].

233   The inertia in response of total and HDL cholesterol concurs with one short-term

234 intervention study using sweet cherries [10]. A lack of impact on blood lipids has also been

235 noted in relation to diet intervention with other anthocyanin-rich berries [30].

236   The current study has several limitations.   It would have been informative to have

237 checked compliance to the intervention through measurement of plasma or urinary

238 anthocyanins. As an adjunct to this, a detailed dietary record would have been informative as

239 to any dietary displacement effects. We narrowly failed to meet our recruitment target of 25

240 participants in each arm. This slightly reduced the power of the study to identify a change in

241 PWV. For CRP, the low sensitivity of the assay (CV 11.5%) may have masked a small anti-

242 inflammatory effect. All biochemical measures were performed in capillary samples collected

243 by finger prick. Limited blood volume meant that we failed to collect complete data for some

244 analytes; this may have contributed to our null effect. It is also possible that our null effect

245 arose because participants may have been too healthy to detect a beneficial effect of cherry

246 juice.   We cannot rule out the possibility that cherry juice may be more effective in

247 individuals with existing hypertension or cardio-metabolic disease.

248   In conclusion our study provides no evidence that a short-term intervention with tart

249 cherry juice reduces arterial stiffness or improves other markers of cardiovascular risk in

250 apparently healthy adults. Confirmation of this null effect is needed, perhaps using longer

251 intervention periods and examining individuals at high risk of cardiovascular disease.

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Table 1 Participant characteristics according to randomisation group at study inclusion (means and SDs)

	Cherry juice (n=25)	Placebo (n=21)
Age (years)	38.3 (6.16)	37.2 (5.78)
Weight (kg)	70.4 (12.75)	69.2 (14.55)
BMI (kg/m^2)	24.6 (3.63)	23.5 (3.00)
Sex (Female/Male)	16/9	13/8

Table 2 Change in outcome variables in the tart cherry juice and control groups over the 6 week intervention period

	Cherry juice		Placebo		Adjusted	
	Baseline	End	Baseline	End	difference#	
	(mean (SD))	(mean (SD))	(mean (SD))	(mean (SD))	(95% CI)	
PWV (m/s)	8.22 (1.69)	8.18 (1.60)	7.98 (1.21)	7.74 (1.06)	0.243	$F (1, 43) =1.564$
n	25		21		(-0.149, 0.634)	$P= 0.218$

365	hsCRP (mg/L)*	1.13 (0.92, 1.38)	1.13 (0.93, 1.03)	1.14 (0.91, 1.43)	1.26 (1.01, 1.59)	-10%**	$F_{(1, 36)} = 1.559$
366	n	22		17		(-14%, 7%)	$P = 0.220$
367	SBP (mm Hg)	110.5 (14.38)	110.2 (12.58)	110.43 (12.28)	113.36 (11.88)	-3.21	$F_{(1, 43)} = 2.019$
368	n	25		21		(-7.763, 1.346)	$P = 0.163$
369	DBP (mm Hg)	70.3 (10.04)	69.2 (9.86)	67.4 (8.28)	69.9 (7.62)	-2.814	$F_{(1, 43)} = 2.496$
370	n	25		21		(-6.406, 0.778)	$P = 0.121$
371	Cholesterol (mmol/L)						
372	Total	4.25 (0.79)	4.22 (0.77)	3.76 (0.67)	4.12 (0.67)	-0.183	$F_{(1, 40)} = 0.926$
373	n	24		19		(-0.569, 0.202)	$P = 0.342$
374	HDL*	0.96 (0.87, 1.05)	1.09 (1.02, 1.16)	1.37 (0.92, 1.15)	1.04 (0.97, 1.11)	7%**	$F_{(1, 36)} = 2.436$
375	n	22		17		(-2%, 16%)	$P = 0.127$
376	FRAP (µM)	1205 (339.45)	1294 (269.03)	1298 (323.05)	1165 (255.55)	173.58	$F_{(1, 39)} = 6.909$
377	n	23		19		(40.002, 307.159)	$P = 0.012$

378

379 [#]Effect of intervention was assessed by ANCOVA adjusted for baseline. *Data was log transformed prior to analysis so baseline and end of

380 study data is expressed as geometric mean and 95% CI. **Adjusted mean difference for log transformed data is expressed as a percentage

381 (Bland 2000).