

1 Title of Article: Dietary Anthocyanins: A Review of the Exercise Performance
2 Effects and Related Physiological Responses
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26 **Abstract**

27 Foods and supplements high in anthocyanins are gaining popularity within sports nutrition.
28 Anthocyanins are pigments within berries and other colourful fruits and vegetables. They have
29 anti-oxidative and anti-inflammatory actions that improve recovery from exercise.
30 Furthermore, anthocyanins can also affect vasoactive properties, including decreasing mean
31 arterial blood pressure and increasing vasodilation during exercise. *In vitro* observations have
32 shown anthocyanin- and metabolite-induced activation of endothelial nitric oxide synthase and
33 human vascular cell migration. However, effects of anthocyanins on exercise performance
34 without a prior muscle-damaging or metabolically demanding bout of exercise is less clear. For
35 example, exercise performance effects have been observed for blackcurrant, but are less
36 apparent for cherry, therefore indicating that the benefits could be due to the specific source-
37 dependent anthocyanins. The mechanisms by which anthocyanin intake can enhance exercise
38 performance may include effects on blood flow, metabolic pathways, and peripheral muscle
39 fatigue, or a combination of all. This narrative review focuses on the experimental evidence for
40 anthocyanins to improve exercise performance in humans.

41 **Keywords:** polyphenols; anthocyanin metabolites; sports nutrition

42

43 **INTRODUCTION**

44 Epidemiological studies have indicated that high intake of dietary polyphenols is associated
45 with lower risk for multiple diseases (Kuriyama et al., 2006; Ivey et al., 2017). Based on
46 chemical structures, there are four groups of polyphenols, i.e. phenolics, flavonoids, stilbenes
47 and lignans, with classes within the groups. Anthocyanins are a class of the flavonoids. The
48 dietary intake of the main anthocyanins are glycosides of their respective aglycones;
49 pelargonidin, cyanidin, delphinidin, peonidin, petunidin and malvidin (Wu et al., 2006).
50 Anthocyanins are water-soluble and act as natural pigments causing purple, blue, red and

51 orange colouration to flowers, leaves, fruits and vegetables. Over 500 different anthocyanins
52 exist, based on structural variety such as the number and position of hydroxyl and methoxyl
53 groups, the specific type and number of bonded sugars, the aliphatic, or aromatic
54 carboxylates bonded to the sugar and the bond position (Speciale et al., 2014).
55 Observational studies indicate a causal link between anthocyanin intake and decreased
56 disease risk, including cardiovascular disease (Cassidy et al., 2016), type-2 diabetes (Muraki
57 et al., 2013) and ageing associated cognitive decline (Letenneur et al., 2007). For many years,
58 benefits were attributed to the anthocyanins scavenging free radicals by B ring hydroxyl
59 groups and conjugated double bonds. However, anthocyanins also affect signalling pathways
60 (Qin et al., 2012), particularly the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway
61 (Cimino et al., 2013; Yan et al., 2017). Nrf2 is a transcription factor regulating gene
62 expression of antioxidant proteins. Oh et al., (2017) observed upregulation of Nrf2 in mice
63 and increased endurance exercise performance, and similar responses may occur in humans.
64 However, such observations have not been made in human studies. Furthermore, effects on
65 blood flow (Matsumoto et al., 2005), blood vessel diameter during exercise (Cook et al.,
66 2017) and endothelial nitric oxide synthase (Xu et al., 2004b) by anthocyanins may all
67 provide mechanisms for improved exercise performance.

68 In a recent systematic review and meta-analysis, polyphenol supplementation for at least 7-
69 days or more increased exercise performance by 1.90% (95% CI 0.40-3.39), with the analysis
70 including studies using quercetin, anthocyanins, epigallocatechin gallate, epicatechin and
71 *trans*-resveratrol (Somerville et al., 2017). This narrative review, however, will focus on the
72 effect of anthocyanin intake by humans on exercise performance. Berry fruits such as
73 blackcurrant, blueberries and raspberries and drupes such as cherry contain high
74 concentrations of anthocyanins, but each with a specific make-up of anthocyanins. For
75 example, the main anthocyanin in blackcurrant is delphinidin-3-rutinoside, whereas in cherry

76 it is cyanidin-3-glucosylrutinoside (Rothwell et al., 2013). In humans, foods containing
77 primarily delphinidin improved metabolic and cardiovascular disease risk biomarkers (Stull
78 et al., 2010; Zhu et al., 2011), whereas cyanidin did not provide the same protective benefits
79 (Curtis et al., 2009; Wright et al., 2013). In addition, delphinidin has a higher potency of
80 activity towards the superoxide radical than cyanidin (Rahman et al., 2006). Therefore,
81 different berries with specific anthocyanin contents may provide different physiological
82 effects, indicating that not all berries may improve exercise performance. This narrative
83 literature review will focus on studies in humans examining the effects of anthocyanin intake
84 on exercise performance and not focus on a specific fruit.

85 **EXERCISE PERFORMANCE**

86 The first study to observe that anthocyanins could be beneficial for exercise performance was
87 published by Willems et al. (2015). Within the study, thirteen trained triathletes (8 males)
88 were supplemented for 7-days with $6 \text{ g}\cdot\text{day}^{-1}$ of New Zealand blackcurrant (NZBC) powder
89 ($\sim 139 \text{ mg anthocyanin}\cdot\text{day}^{-1}$) dissolved in 140 mL of water before completing an incremental
90 cycle ergometer test. NZBC powder caused a downward shift of the lactate curve during
91 incremental intensity cycling with lower plasma lactate at 40, 50, 60 and 70% of maximum
92 power. In addition, the intensity at $1 \text{ mmol}\cdot\text{L}^{-1}$ lactate rise was 4% higher (placebo: 184 ± 52
93 vs. blackcurrant: $192\pm 52 \text{ W}$) and the intensity at $4 \text{ mmol}\cdot\text{L}^{-1}$ was 6% higher (placebo:
94 223 ± 57 vs. blackcurrant: $236\pm 60 \text{ W}$). There was no difference in heart rate and oxygen
95 uptake at the pre-defined reference points (i.e. 1 and $4 \text{ mmol}\cdot\text{L}^{-1}$), and diastolic, systolic,
96 mean arterial pressure, heart rate, stroke volume, cardiac output and total peripheral
97 resistance during the incremental exercise. Maximum oxygen uptake ($\dot{V}\text{O}_{2\text{max}}$) (placebo:
98 49.1 ± 6.2 vs. blackcurrant $49.7\pm 6.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and maximum power output at $\dot{V}\text{O}_{2\text{max}}$
99 (placebo: 305 ± 68 vs. blackcurrant $307\pm 62 \text{ W}$) were also not different. These results show no
100 effect of blackcurrant on the oxygen cost of the exercise, $\dot{V}\text{O}_{2\text{max}}$ or maximum power ability,

101 however, lactate observations suggest that exercise performance could be enhanced by
102 blackcurrant anthocyanins.

103 Cook et al. (2015) examined the effects of blackcurrant anthocyanins on exercise
104 performance in a 16.1 km cycling ergometer time-trial. Following 7-days intake of
105 blackcurrant extract capsules (105 mg anthocyanin·day⁻¹) in 14 trained male cyclists, the
106 study observed a 2.4% faster 16.1 km time ($P=0.027$) with blackcurrant (placebo 1722±131
107 vs blackcurrant 1678±108 s). There have been similar observations of increased exercise
108 performance following 7-days intake of blackcurrant extract in different exercise models. For
109 example, Perkins et al. (2015) observed an increase of 10.6% ($P=0.023$) in total running
110 distance during an incremental intermittent high-intensity running protocol to exhaustion on a
111 treadmill (placebo 3871±622 vs. blackcurrant 4282±833 m) and Murphy et al. (2017)
112 observed an increased performance of 0.82% ($P=0.034$) for a repeated 4 km cycling time-trial
113 (placebo 771±60 vs. blackcurrant 764±56 s), but sample size could have been a limitation to
114 allow firm conclusions for each of the two separate 4 km tests. Increased resistance to fatigue
115 during exercise has also been shown following intake of blackcurrant extract with less
116 slowing of maximal sprint running in the last 15-minute block of the Loughborough
117 Intermittent Shuttle Test (Willems et al., 2016). The positive effects of blackcurrant extract
118 on exercise performance have been identified in trained cyclists (Cook et al., 2015; Murphy
119 et al., 2017; Willems et al., 2015), active but untrained males (Perkins et al., 2015; Willems et
120 al., 2016) and trained youth footballers (Godwin et al., 2017). The effects in elite athletes are
121 unknown and need to be examined in future research, especially in those with a relatively low
122 anthocyanin intake. It has been recently shown that baseline antioxidant status can be a
123 determinant in the effectiveness of supplementing with antioxidants. For example, individuals
124 with a low baseline status of vitamin C (Paschalis et al., 2016) and glutathione (Paschalis et
125 al., 2018) improved their $\dot{V}O_{2\max}$ following supplementation with vitamin C and N-

126 acetylcysteine, respectively, however those with higher baseline levels did not respond. In
127 addition, all these performance studies except Willems et al. (2015) used men, therefore
128 studies in women are needed to confirm no differences between the sexes. A recent study by
129 Strauss et al. (2018) replicated for females findings by Cook et al. (2017) in males of
130 increased fat oxidation by New Zealand blackcurrant during 120-minutes cycling at 65%
131 $\dot{V}O_{2max}$, therefore increased exercise performance from blackcurrant anthocyanins in females
132 is likely.

133 The effects of other high anthocyanin content fruits on exercise performance are less clear
134 though. For example, cherry has received considerable interest for its effects on recovery
135 (Bell et al., 2014; Bell et al., 2016; Bowtell et al., 2011; Connolly et al., 2006; Howatson et
136 al., 2010), however there is limited evidence on its potential to increase exercise performance
137 without a mechanically damaging or metabolically fatiguing protocol (Table 1).

138 The first study to examine the effect of cherry anthocyanins on exercise performance was by
139 Clifford et al. (2013). The study compared 120 mg Pycnogenol[®] (citrus bioflavonoids), 200
140 mg CherryActive[®] and placebo (200 mg maltodextrin) on 20 km cycle ergometer time-trial
141 performance in nine moderately trained triathletes and cyclists. Participants were
142 supplemented for 2-days before and on the day of the time-trial, with results showing no
143 difference between the conditions (Pycnogenol[®]: 1990.07 ± 93.18 vs. CherryActive[®]:
144 2008.56 ± 97.50 vs. placebo: 2030.30 ± 124.73 s). However, the *P*-value of 0.117 suggests it
145 was approaching a trend for a performance effect and the sample size of nine subjects may
146 therefore indicate that the study was underpowered to allow a firm conclusion. In a study by
147 Howatson et al. (2010) to examine the effects of cherry juice on recovery following marathon
148 running, a secondary measure identified if there was any influence on marathon running
149 performance (i.e. finish times) in recreational marathon runners. Supplementing two groups
150 matched for their predicted finish time with a short intake (5-days) before the marathon with

151 cherry juice (~40 mg·day⁻¹ anthocyanins) or placebo allowed comparison between the groups
152 on their marathon performance. The study observed no difference in marathon finishing time
153 for the two conditions, however, the difference between the actual and predicted finish time
154 was smaller for the cherry group (predicted: 3:41:00±0:26:01 vs. actual: 3:48:04±0:48:48
155 h:min:s) than the placebo group (predicted: 3:56:40±0:40:37 vs. actual: 4:15:48±1:01:22
156 h:min:s), although this was not significantly different. However, sample size may have been
157 an issue in Howatson et al. (2010) to not showing a significant beneficial effect for the cherry
158 juice. In a similar study, Levers et al. (2016) used endurance trained runners and split them in
159 two matched groups on predicted race pace (from results of previous year). The study
160 supplemented in a double-blind design with a powdered form of tart cherry skins (66 mg·day⁻¹
161 anthocyanins) or placebo for 7-days prior and on the day of a half marathon, in turn,
162 allowing comparison on exercise performance in the race. Half-marathon finish time was
163 13% faster ($P=0.001$) in the cherry group (cherry: 103±9.28 vs. placebo: 118±9.72 minutes).
164 However, within the studies by Howatson et al. (2010) and Levers et al. (2016), there was no
165 cross-over condition, therefore, it is difficult to determine if exercise performance was
166 improved by cherry in those studies.

167 What is more, in the studies by Howatson et al. (2010) and Levers et al. (2016), the exercise
168 durations were long, and therefore the exercise intensities are likely lower than those of the
169 blackcurrant studies with short duration exercise periods of Cook et al. (2015), Murphy et al.
170 (2017), Perkins et al. (2015) and Willems et al. (2016). Anthocyanins have been shown to
171 increase vasodilation and cardiac output (Cook et al., 2017) and peripheral blood flow in the
172 forearms (Matsumoto et al., 2005). Alterations in blood flow may benefit exercise
173 performance where the intensity results in an imbalance of perfusion to support metabolism
174 and causes a decrease in intramuscular oxygen partial pressure (Bylund-Fellenius et al., 1981)
175 and acidic conditions (Costill et al., 1983) such as those during high intensity exercise.

176 Recently, Keane et al. (2018) was the first study to examine the effects of an acute intake of
177 cherry on exercise performance. They observed 60 mL Montmorency cherry juice containing
178 ~60 mg anthocyanins to have no effect on cycling time-to-exhaustion during severe intensity
179 exercise (CherryActive®: 772 ± 32 vs. placebo: 733 ± 32 s, $P=0.323$), however in a 60-s all-out
180 sprint following the time-to-exhaustion, cherry increased peak power by 9.5%
181 (CherryActive®: 363 ± 42 vs placebo: 330 ± 26 W, $P=0.034$) and total work by 10%
182 (CherryActive®: 21 ± 3 vs. 19 ± 3 kJ, $P=0.021$).

183 The studies by Cook et al. (2015), Godwin et al. (2017), Murphy et al. (2017), Perkins et al.
184 (2015) and Willems et al. (2016) observed blackcurrant extract taken for 6-days before and
185 on the morning of the seventh-day, 2-hours before performance testing, with Keane et al.
186 (2018) supplementing cherry acutely 90-minutes before. This raises questions if the
187 performance benefits are entirely affected by intake of last dose, or a result of the previous 6-
188 days intake. Furthermore, the plasma metabolites by anthocyanin intake are likely key to the
189 observed performance and physiological responses. For example, following a 500 mg intake
190 of cyanidin-3-glucoside, Czank et al. (2013) observed a peak concentration of 0.14 ± 0.05
191 $\mu\text{mol/L}$ and area under the curve in 48-hours of 0.31 ± 0.13 $\mu\text{mol}\cdot\text{h/L}$ for cyanidin-3-
192 glucoside, while the metabolite hippuric acid had a peak concentration of 1.96 ± 1.39 $\mu\text{mol/L}$
193 and area under the curve in 48-hours of 46.42 ± 30.31 $\mu\text{mol}\cdot\text{h/L}$. Therefore, bio-accumulation
194 of metabolites including phase II conjugates (Czank et al., 2013) by anthocyanin intake over
195 7-days is possible and may have been required to cause the exercise performance benefits. In
196 an animal study by Kirakosyan et al. (2015), three weeks of cherry feeding resulted in diverse
197 tissue distribution of anthocyanins. To the author's knowledge, no studies have examined if
198 bio-accumulation of metabolites and diverse tissue distribution of anthocyanins in human
199 occurs following multiple days intake of anthocyanins. However, Kalt et al. (2014) observed
200 that following an intake of 250 mL of blueberry juice, metabolites of anthocyanins are still

201 present in urine 5-days following no further intake of anthocyanins. Most interestingly,
202 metabolites from the anthocyanin pelargonidin were present, which were not in the blueberry
203 juice, which may indicate dihydroxylation and demethylation of anthocyanin by xenobiotic
204 and colonic bacteria (Kalt et al., 2014).

205 It is likely that the efficacy of anthocyanin supplementation on exercise performance without
206 a prior fatiguing bout will depend on several inter-related factors. Firstly, the subjects training
207 status, age, health, habitual anthocyanin consumption and expression of genes. Secondly, the
208 dose and duration of intake, the specific anthocyanins consumed and/ or the food source of
209 anthocyanins consumed. Lastly, the intensity, duration and type of exercise. An acute intake
210 may influence cardiovascular alterations, such as vasodilation (Cook et al., 2017) and
211 increased peripheral blood flow (Matsumoto et al., 2005), but longer intake durations may be
212 required to result in changes in cellular signalling [see below for discussion].

213 **TRAINING RESPONSES**

214 While benefits to exercise performance following a short duration of intake of anthocyanins
215 have been observed (Table 2) (Cook et al., 2015; Godwin et al., 2017; Keane et al 2018;
216 Murphy et al., 2017; Perkins et al., 2015; Willems et al., 2016) the effects of regular intake on
217 training adaptations are an important consideration. Blunting of training adaptations has been
218 observed following a high intake of antioxidants, and it is possible that the blunting requires
219 an intake threshold. For example, vitamin C intake of 200 mg·day⁻¹ can be justified for health
220 reasons, though an intake of >1000 mg·day⁻¹ appears to blunt training adaptations by limiting
221 mitochondrial biogenesis and possibly altering vascular function (Braakhuis et al., 2012). It is
222 not known if anthocyanins can have the same effects, however, cyanidin-3-glucoside have
223 been shown to increase gene expression for sirtuin 1 and proliferator-activated receptor
224 gamma coactivator-1 α (PGC1- α) in myotubes (Matsukawa et al., 2015). PGC1- α activation is
225 required for mitochondrial biogenesis in skeletal muscle (Islam et al., 2018). Anthocyanins

226 also increased activation of AMP-activated protein kinase and expression of PGC1- α in mice
227 hepatocytes with non-alcoholic steatohepatitis (Tang et al., 2015). Extrapolation of these
228 findings to human muscle during a period of physical training could provide positive benefits
229 of regular anthocyanin intake on training adaptations. However, this is speculative, therefore
230 further research on combined effects of anthocyanin intake and physical training on
231 biological adaptations is required.

232 Braakhuis et al. (2014) also examined the influence of blackcurrant on 5 km road running
233 time-trial and an incremental treadmill test to exhaustion following supplementation during a
234 training period in female runners. Using a randomised, three-condition, cross-over placebo-
235 controlled design, twenty-three trained female runners consumed 250 mL of fruit drink
236 concentrate mixed with blackcurrant juice powder twice daily providing 300 mg·day⁻¹ of
237 anthocyanins and vitamin C mixed with fruit juice or placebo. Intake was for 24-days while
238 undergoing high intensity running training controlled for estimation of the training impulse
239 with a washout of 26 days between conditions. There were no effects on 5 km time-trial
240 performance, however during the incremental test to exhaustion, they reported with
241 inferential statistics (with 90% confidence limits) a possible improvement of 1.9±2.5% for
242 the fastest runners by 1 SD and 2.3±3.6% for the runners faster by 2 SD (i.e. runners faster by
243 1 and 2 SD of mean speed on an incremental running test, respectively) for the blackcurrant
244 condition. Interestingly, the average runners in the cohort had no change in performance
245 following the training and supplementation period and were possibly slower. In addition,
246 Godwin et al. (2017) observed also the beneficial effect of blackcurrant on sprint
247 performance in more highly trained football players.

248 Controlling a 6-week training period of treadmill and cycle exercise (3 times a week, 60-90
249 min) so that participants started at 60-65% of maximum heart rate and progressed to 75-85%
250 of maximum heart rate by the end of the training period, Yarahmadi et al. (2014) used a

251 double-blind randomised design to supplement with 100 mg·day⁻¹ anthocyanin capsules (food
252 source and individual anthocyanins not stated) or placebo across the training period in active
253 (>3 years history of athletic training) males and females. Following the training period, the
254 anthocyanin group increased their $\dot{V}O_{2\max}$ (anthocyanin pre: 48.65±4.73, post: 52.62±5.04
255 mL·kg⁻¹·min⁻¹), whereas the placebo group did not (placebo pre: 49.88±5.23, post:
256 49.61±5.33 mL·kg⁻¹·min⁻¹). However, as $\dot{V}O_{2\max}$ is only an indicator of endurance exercise
257 performance potential, it is not possible to state that endurance performance can improve
258 from training while supplementing with anthocyanins.

259 To the author's knowledge, these are the only studies to have used anthocyanin
260 supplementation during training. As there was no detriment in performance in either study
261 following intake of blackcurrant anthocyanins compared to placebo, it is likely that for these
262 doses and conditions, there is no suppression of training responses despite the anti-oxidative
263 properties of anthocyanins. However, further research is recommended on high doses and
264 prolonged intakes of anthocyanins during controlled training periods to identify if negative
265 responses can occur.

266 **RECOVERY RESPONSES**

267 Many studies examined the effects of anthocyanins on markers of oxidative stress (e.g.
268 thiobarbituric acid reactive substances, total antioxidant status, lipid hydroperoxides and
269 protein carbonyls) and inflammation (e.g. interleukin 6, tumour necrosis factor α , C-reactive
270 protein) following muscle-damaging and metabolically demanding exercise (Bell et al., 2014;
271 Bell et al., 2015; Bell et al., 2016 ; Howatson et al., 2010). Identifying marker responses
272 during recovery is outside the scope of this review, however, we will address effects of
273 anthocyanins on the functional recovery from muscle-damaging and/or fatiguing exercise.
274 To the best of our knowledge, Connolly et al. (2006) was the first study to observe that
275 anthocyanins could be beneficial for recovery. Using a single blind crossover design, male

276 students were supplemented with Montmorency cherry juice mixed with apple juice, each
277 intake containing at least 40 mg anthocyanins for 9-days (4-days pre, day of and 4-days post
278 exercise), or the placebo of black cherry soft drink mixed with water. In the 96 hours
279 following a muscle damaging protocol of the elbow flexors, Montmorency cherries showed
280 significant attenuation ($P<0.0001$) in the decline of isometric strength compared to placebo
281 (4% vs. 22%, respectively). Similarly, Bowtell et al. (2011) demonstrated for well-trained
282 males in a double-blind crossover design that 10-days of Montmorency cherry containing
283 $\sim 234 \text{ mg}\cdot\text{day}^{-1}$ anthocyanin (7-days pre, on the day and 2 days post exercise) resulted in a
284 more rapid recovery ($P=0.04$) of isokinetic knee extensor force than the placebo (i.e. fruit
285 concentrate) following an eccentric-induced muscle damage protocol of 100 knee extension
286 at 80% of one-repetition maximum. McLeay et al. (2012) also observed that anthocyanins
287 from a New Zealand Blueberry smoothie ($\sim 97 \text{ mg}$ anthocyanin per smoothie), taken 5 and 10
288 hours prior to a bout of eccentric isokinetic contractions of the knee extensors and 12 and 36
289 hours post bout, were associated with a faster rate of recovery of isometric peak torque 36
290 hours post bout in physically active females ($P=0.047$). While these three studies have
291 observed ergogenic effects on the recovery of muscle function following eccentric exercise-
292 induced muscle damage, the results should be taken with caution. The studies used crossover
293 designs so that the participants completed the experimental exercise protocol on two visits.
294 This was achieved by exercising the contralateral limb in the second visit. In addition,
295 repeated eccentric exercise is known for the repeated bout effect, whereby a second bout of
296 eccentric exercise experiences a protective effect on damage and muscle function (McHugh
297 et al., 1999). Protective effects may happen as well to the contralateral limb not previously
298 exposed to eccentric exercise (Howatson and van Someren, 2007; Starbuck and Eston, 2012).
299 Therefore, matched groups or sufficient time between sessions would be a better study design

300 to examine these responses. However, the crossover design ensures that the digestion and
301 bioavailability of anthocyanins will likely remain constant between visits.

302 Using matched groups, by assigning participants to experimental conditions (i.e. cherry juice
303 or placebo) based on predicted marathon finish time, Howatson et al. (2010) showed that in
304 the 48-hours post-marathon, the recovery of maximal voluntary isometric force of the knee
305 extensors was improved ($P<0.024$) with the total intake of cherry juice 5 days before, on the
306 day of the marathon and 48-hours post-marathon. However, decrements in maximal
307 voluntary isometric force immediately following the marathon were similar (cherry: 24.3%
308 vs. placebo: 26.9%) indicating that cherry anthocyanins ($80 \text{ mg}\cdot\text{day}^{-1}$) do not affect muscle
309 damage and fatigue sustained from the marathon.

310 Bell et al. (2014) examined in trained cyclists the responses of Montmorency cherry extract
311 on multiple bouts of 109 minutes stochastic road cycling simulation with intake 4-days pre-
312 cycling and 3 consecutive days of time-trials with supplementation. While a decrease in total
313 work performed was observed across the three time-trial days, there was no difference
314 between Montmorency cherry extract or placebo on total work performed indicating no effect
315 on repeated cycling performance over several days. A further study by Bell et al. (2015)
316 examined the recovery responses 72 hours following one bout of the same 109 minutes
317 stochastic road cycling simulation and demonstrated that maximal voluntary isometric
318 contraction of the knee extensors was significantly attenuated with Montmorency cherry
319 versus placebo, with between-group differences of 10%, 12% and 21% at 24, 48 and 72 hours
320 post bout, respectively. This was the first study to highlight that anthocyanins were associated
321 with maintenance of muscle function following exercise that did not include damage by
322 eccentric contractions such as those of Bowtell et al. (2011), Connolly et al. (2006),
323 Howatson et al. (2010) and McLeay et al. (2012). Bell et al. (2016) examined further the
324 attenuation of muscle function following another exercise simulation, this time adapting the

325 Loughborough Intermittent Shuttle Test to standardise the distance covered by all participants
326 (the original protocol requires running to exhaustion). Maximal voluntary isometric force of
327 the knee extensors was maintained with Montmorency cherry at 24, 48 and 72 hours
328 following the exercise, with a peak difference between placebo and cherry of 19% occurring
329 48-hours post bout. Performance in other functional measurements such as the counter
330 movement jump, 5-0-5 agility test and 20-metre sprint time, were also all attenuated with
331 cherry within the recovery period. Taken together, these studies indicate that supplementation
332 with anthocyanins from cherry protect against declines in muscle function following
333 strenuous activity and has positive effects on subsequent functional recovery after damaging
334 or fatiguing exercise.

335 **MECHANISMS**

336 The mechanisms for increased exercise performance by anthocyanin intake have not been
337 fully elucidated, however may result from alterations in blood flow. For example, Matsumoto
338 et al. (2005) observed in a maximal voluntary contraction (MVC) of the trapezius muscle
339 following 30-minutes of typing a change in total haemoglobin (measured by near-infrared
340 spectroscopy) within the muscle of $106.0 \pm 12.8\%$ of the pre-value following blackcurrant
341 concentrate capsules, however following placebo it decreased to $53.2 \pm 21.6\%$. Furthermore,
342 Cook et al. (2017) observed during a 120-second isometric contraction of the knee extensors
343 at 30% of MVC that the femoral artery diameter of the exercising limb was between 6.9 and
344 8.2% larger following 7-day intake of New Zealand blackcurrant extract. This was also
345 coupled with a decrease in activation of the *vastus medialis muscle*, a decrease in total
346 peripheral resistance and an increase in cardiac output during the contraction (Cook et al.,
347 2017).

348 In the studies of Cook et al. (2015, 2017), it was reported how many of the participants had a
349 change in exercise performance and femoral artery diameter following blackcurrant extract

350 intake, respectively. In both studies ~80% of the participants responded to the New Zealand
351 blackcurrant intake and it could be possible that changes in exercise performance and blood
352 flow alterations by anthocyanins are associated with genotype. For example, George et al.
353 (2012) examined the effect of a high flavonoid fruit and vegetable drink on vasodilation
354 within the forearm (measured by Laser Doppler with iontophoresis) 180-minutes following
355 intake. Vasodilation in the forearm following consumption was different for those with
356 different expressions of the endothelial nitric oxide synthase (eNOS) gene Glu298Asp,
357 whereby there was higher endothelium-dependent vasodilation in response in GG individuals
358 compared to GT. Interestingly, plasma nitrate and nitrite increased from baseline following
359 intake for both genotypes, however there was no difference between the genotypes in the
360 amount. The metabolite hippuric acid also increased for both genotypes, indicating that the
361 polyphenols within the flavonoid drink were absorbed and metabolised, however, at 300-
362 minutes post intake for those with GG expression, there was approximately a 120% increase
363 from baseline, whereas for the GT expression this increase was approximately 500% from
364 baseline. The cause for this large difference is unknown, however may result from the gut
365 microflora which are responsible for converting polyphenols to phenolic acids.

366 If an alteration in blood flow is a causal factor for improved exercise performance, then
367 increasing availability of nitric oxide could be the mechanism. *In vitro* cyanidin-3-glucoside
368 has been shown to up-regulate eNOS (Xu et al., 2004a, Xu et al., 2004b; Sorrenti et al.,
369 2007). This was observed using cultured endothelial cells at concentrations from 0.001 to 250
370 μM . However, Czank et al. (2013) and de Ferras et al. (2014) have confirmed a physiological
371 range of anthocyanin metabolites in humans of 0.1 – 10 μM . Using doses of 0.1, 1 and 10
372 μM , Edwards et al. (2015) observed differential activity between the whole-body anthocyanin
373 and metabolites, with cyanidin-3-glucoside up-regulating eNOS on every dose, but the
374 metabolites protocatechuic acid and vanillic acid having no influence at any dose within a

375 human vascular cell model. However, the metabolites can maintain vascular homeostasis by
376 increasing nitric oxide bioactivity through mechanisms involving NADPH inhibition or
377 inducing cytoprotective enzyme haem oxygenase-1, an enzyme that catalyzes the degradation
378 (Edwards et al., 2015). Interestingly, Keane et al. (2016a) observed no *in vivo* increase in
379 plasma nitrate and nitrite (i.e. proxy markers of eNOS activity) following intake of
380 Montmorency cherry concentrate, yet Keane et al. (2016b) observed a combination of the
381 anthocyanin metabolites protocatechuic acid and vanillic acid to increase human vascular
382 smooth muscle cell migration *in vitro*. Therefore, the metabolites of the anthocyanins are
383 likely key to the vascular effects observed. So far only a few metabolites have been examined
384 for their effects, yet it is worth noting that Czank et al. (2013) observed 24 metabolites from
385 the anthocyanin cyanidin-3-glucoside in human serum. As a result, this indicates many
386 metabolites, alone and in combination, have to be examined for cardiovascular bioactivity
387 rather than the few which have currently been studied.

388 **LIMITATIONS AND FUTURE CONSIDERATIONS**

389 The anthocyanin content of berry fruits is heavily influenced by growing conditions. For
390 example, ultraviolet light exposure (i.e. sun light) is one of the biggest predictors of
391 concentrations of anthocyanins (Guo et al., 2008). Therefore, to get a similar intake of
392 anthocyanin from berries grown in different countries needs different amounts to be
393 consumed. In addition, the cultivar of the berry is influential in the anthocyanin concentration
394 (Moyer et al., 2002). The ripeness can also effect the anthocyanin content, with riper fruit
395 containing higher levels than partially ripe fruit. For example, Gonçalves et al. (2004)
396 observed in partially ripe cherries the anthocyanin concentration to be very low (5 to 23
397 mg/100 fresh weight), yet the ripe fruits have substantially higher concentrations (19 to 96
398 mg/100 fresh weight). Another factor to consider is that berry fruits are also seasonal,
399 implying that intake from food sources is likely harder during winter. The doses of

400 anthocyanins used within the studies discussed in this review indicate that to get a similar
401 intake from foods would result in a large portion. For example, Cook et al. (2015)
402 supplemented with 105 mg New Zealand blackcurrant capsules for 7-days, which is
403 equivalent to ~80 blackcurrants per day, while Howatson et al. (2010) supplemented with
404 ~455 mL (16 fl oz) cherry juice containing 80 mg anthocyanins and equivalent to 120
405 cherries per day. For the sports nutritionist, manufactured products provide an ideal and
406 convenient source of dietary anthocyanins for supplementation to improve performance.
407 These can include powders, drinks and encapsulated powders, which with a known dose of
408 anthocyanins in the products provide a reliable intake that can be used throughout the year,
409 despite seasonal supply issues.

410 To the author's knowledge, there have been no studies that have compared the exercise
411 performance effects of different berries with specific anthocyanin profiles. Future studies
412 should also ensure to be conducted with appropriate sample sizes. It is possible that some
413 published berry studies lacked sufficient power to allow firm conclusions on berry effects.
414 However, it is known that anthocyanins, anthocyanin metabolites and other polyphenols can
415 act synergistically (Shanmuganayagam et al., 2002; Dai et al., 2009), therefore appropriate
416 dietary controls would be needed to determine these factors. Some studies have addressed
417 this by using wash-out diets void of all anthocyanins (Bell et al., 2014; 2015; 2016). The use
418 of wash-out diets allows the study design to control for these potential interactions, however
419 it is problematic for ecological validity. In addition, by removing polyphenols from the diet,
420 it is possible that the potential for change is reduced or even increased (Paschalis et al. 2018)
421 and it could be argued that the ergogenic effects are only of interest when they can be
422 observed imposed on top of normal dietary intake, for example in the design used by Levers
423 et al. (2016).

424 **CONCLUSION**

425 The use of anthocyanin containing products indicate that exercise performance benefits may
426 be fruit and/or berry specific. Performance benefits have been observed following
427 blackcurrant ingestion, whereas performance improvements following intake of other
428 anthocyanin containing fruits have not been demonstrated to the same extent. This may be
429 due to the individual and specific anthocyanin make ups within the fruits and future work is
430 needed to confirm this. Future work is also needed to identify if suppression of training
431 responses occurs, however current evidence indicates no detriment to performance when
432 anthocyanins are taken during training. The mechanisms for improved exercise performance
433 may result from increases in blood flow, while training adaptations may be influenced by
434 alterations in cellular signalling and faster recovery through antioxidative and anti-
435 inflammatory pathways.

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439 **Conflicts of interest**

440 The authors declare no conflict of interest.

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684 Table 1. Summary of studies examining the effect of cherry anthocyanins on exercise performance.

Reference	Participant characteristics; design	Anthocyanin source; dose	Duration of intake	Timing of last dose before exercise	Performance protocol	Performance
Clifford et al. (2013)	9 moderately trained triathletes and cyclists, placebo controlled with counterbalanced crossover and double-blind	CherryActive®; NR	2-days	2-3 hours prior	Cycling; 20 km time-trial	No change <i>P</i> = 0.117
Levers et al. (2016)	27 endurance trained runners or triathletes (<i>n</i> =18 M); placebo controlled with randomised allocation after participants matched and double-blind	480 mg Montmorency tart cherry skin powder capsule; 66 mg·day ⁻¹	7-days prior, day of and 2-days following	NR	Half-marathon running on closed course	Cherry had faster finish time <i>P</i> = 0.001
Keane et al. (2018)	10 trained male cyclists; placebo controlled with randomised crossover and double-blind	60 mL Montmorency cherry juice; 60 mg	1-day	90-minutes	Cycling; 60-s sprint following 6-min severe intensity cycling test	↑10% of total work during 60-s sprint, <i>P</i> = 0.021

685 NR; Not reported,

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Table 2. Summary of studies examining the effect of blackcurrant anthocyanins on exercise performance.

Reference	Participant characteristics; design	Anthocyanin source; dose	Duration of intake	Timing of last dose before exercise	Performance protocol	Performance
Willems et al. (2015)	14 trained triathletes ($n = 8$ M); placebo controlled with randomised crossover and double-blind	6 g New Zealand blackcurrant powder in 140 mL of water; 138.6 mg·day ⁻¹	7-days	2 hours prior	Cycling; step protocol @ 30 W·min ⁻¹	No change, $P > 0.05$
Cook et al. (2015)	14 trained male cyclists; placebo controlled with randomised crossover and double-blind	300 mg New Zealand blackcurrant extract capsule; 105 mg·day ⁻¹	7-days	2 hours prior	Cycling; 16.1 km time-trial	Time to complete time-trial ↓2.4%, $P = 0.03$
Perkins et al. (2015)	13 recreationally active males; placebo controlled with randomised crossover and double-blind	300 mg New Zealand blackcurrant extract capsule; 105 mg·day ⁻¹	7-days	2 hours prior	Treadmill Running; stages of 6x19 s sprints interspersed with 50% $\dot{V}O_{2max}$ for 15 s. Stage 1 started at 80% $\dot{V}O_{2max}$ and increased by 5% $\dot{V}O_{2max}$ each stage, then 2.5% $\dot{V}O_{2max}$ after 110% $\dot{V}O_{2max}$.	Running distance during sprints ↑10.8% $P = 0.02$
Murphy et al. (2017)	10 male trained cyclists; placebo controlled with crossover and double-blind	300 mg New Zealand blackcurrant capsule; 105 mg·day ⁻¹	7-days	2 hours prior	Cycling; 4 km time-trial followed by 10-minutes rest and another 4 km time-trial	Total time for both time-trials ↓0.82%, $P=0.034$
Godwin et al. (2017)	15 recreationally active and nine trained youth players; placebo controlled with randomised crossover and double-blind	600 mg New Zealand blackcurrant extract capsules; 210 mg·day ⁻¹	7-days	2 hours prior	Running Based Anaerobic Sprint Test	Reduced slowing of sprint 5, $P = 0.02$

696 NR; Not reported, $\dot{V}O_{2max}$; maximal aerobic capacity, $v\dot{V}O_{2max}$; velocity at maximal aerobic capacity.

