

Antioxidants for preventing and reducing muscle soreness after exercise: a Cochrane systematic review

Mayur K Ranchordas¹, David Rogerson¹, Hora Soltani², Joseph T Costello³

1 - Academy of Sport & Physical Activity, Sheffield Hallam University,
Sheffield, UK.

2 - Centre for Health and Social Care Research, Sheffield Hallam University,
Sheffield, UK.

3 - Department of Sport and Exercise Science, University of Portsmouth,
Portsmouth, UK

[Corresponding author: Dr Mayur K. Ranchordas, Academy of Sport &
Physical Activity, Faculty of Health & Wellebing, Sheffield Hallam University,
Sheffield, S10 2BP - \[m.ranchordas@shu.ac.uk\]\(mailto:m.ranchordas@shu.ac.uk\)](#)

Abstract

Objective

To determine whether antioxidants supplements and antioxidant-enriched foods can prevent or reduce delayed onset muscle soreness after exercise.

Methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, SPORTDiscus, trial registers, reference lists of articles and conference proceedings up to February 2017

Results

In total, 50 studies were included in this review which included a total of 1089 participants (961 were male and 128 were female) with an age range between 16 and 55 years. All studies used an antioxidant dosage higher than the recommended daily amount. The majority of trials (47) had design features that carried a high risk of bias due to selective reporting and poorly described allocation concealment, potentially limiting the reliability of their findings. We rescaled to a 0 to 10 cm scale in order to quantify the actual difference between groups and we found that the 95% CIs for all five follow-up times were all well below the minimal important difference of 1.4 cm: up to 6 hours (MD -0.52, 95% CI -0.95 to -0.08); at 24 hours (MD -0.17, 95% CI -0.42 to 0.07); at 48 hours (MD -0.41, 95% CI -0.69 to -0.12); at 72 hours (MD -0.29, 95% CI -0.59 to 0.02); and at 96 hours (MD -0.03, 95% CI -0.43 to 0.37). Thus, the effect sizes suggesting less muscle soreness with

antioxidant supplementation were very unlikely to equate to meaningful or important differences in practice.

Conclusions

There is moderate to low-quality evidence that high dose antioxidant supplementation does not result in a clinically relevant reduction of muscle soreness after exercise at up to 6 hours or at 24, 48, 72 and 96 hours after exercise. There is no evidence available on subjective recovery and only limited evidence on the adverse effects of taking antioxidant supplements.

1 Introduction

2

3 Delayed onset muscle soreness (DOMS) typically occurs after
4 strenuous and unaccustomed exercise and physical activity. It is classified
5 as a grade 1 muscle strain injury and is characterised by localised
6 tenderness and soreness.¹ Depending on the severity of exercise, DOMS
7 typically peaks between 24 to 72 hours after a bout of exercise but
8 eventually disappears after five to seven days.²⁻⁷ DOMS could be
9 detrimental for athletes who are returning to training from a prolonged
10 period of inactivity. In addition, DOMS could deter individuals from
11 adhering to an exercise programme. For some individuals, DOMS could
12 result from excessive physical activity associated with daily living,
13 particularly if repeated eccentric movements or unaccustomed physical
14 activity are involved.

15

16 Several theories have been proposed to explain the mechanisms
17 underlying DOMS. These include lactate accumulation,⁸ inflammation,⁹
18 muscle spasm,¹⁰ muscle damage,¹¹ connective tissue damage,¹² and
19 increased muscle temperature.¹³ A common feature of several of these
20 proposed mechanisms is an increased production of free radicals,¹⁴ and
21 reactive oxygen species. Indeed, it has been shown that reactive oxygen
22 species are produced in nearly every biological process and that they also
23 play a crucial role as signalling molecules for translating the exercise signals
24 to appropriate adaptations.¹⁵

25

26 The rationale for taking antioxidant supplements after exercise to
27 reduce DOMS comes from the notion that they could reduce the negative

28 effects of reactive oxygen species and oxidative stress resulting from
29 exercise.¹⁶ Oxidative stress could deplete the body's antioxidant defences
30 and increase the rate of free radical production.¹⁷⁻¹⁹ Moreover,
31 unaccustomed, eccentric and exhaustive exercise may also induce
32 inflammatory reactions which can contribute to increased reactive oxygen
33 species production and reduced antioxidant defences.²⁰ These can cause
34 exercise-induced muscle damage and result in DOMS.¹ Dietary antioxidants
35 may counteract oxidative stress by reducing the production of free radical
36 and reactive oxygen species associated with exercise.¹⁷ Reducing DOMS
37 could be beneficial to athletes when returning to training from injury (i.e.
38 after a period of inactivity), and it could help sedentary and older
39 individuals recover from unaccustomed physical activity.

40
41 The ease of taking antioxidant supplements to prevent and reduce
42 muscle soreness after exercise and enhance recovery makes it an attractive
43 option for physically active individuals. Moreover, antioxidant supplements
44 are available to buy from supermarkets and health food stores and some
45 are marketed to enhance recovery. Despite the popularity of antioxidant
46 supplements, the evidence supporting its used is mixed.²¹⁻²³ Therefore, the
47 objective of this systematic review was to determine whether antioxidant
48 supplements and antioxidant-enriched foods could prevent or reduce
49 DOMS after exercise.

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55 **Methods**

57 **Inclusion criteria**

59 Any randomised controlled trials or quasi-randomised controlled
60 trials investigating the effects of dietary antioxidants on preventing or
61 reducing delayed onset muscle soreness were considered for this meta-
62 analysis.

64 **Search strategy**

66 A systematic search of the literature was conducted in the
67 Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the
68 Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE,
69 Embase and SPORTDiscus, current to February 2017 was performed by two
70 authors. ClinicalTrials.gov and the World Health Organization Clinical Trials
71 Registry Platform were also searched for any ongoing or recently
72 completed studies. Experts in the field were also contacted to find
73 unpublished trials. The reference list of all included studies and relevant
74 reviews were also screened for further references to relevant trials. No
75 language restrictions were applied.

77 **Data extraction**

79 Two authors independently extracted data using a customised form.
80 We resolved any disagreements by consultation with the other authors. In

81 some cases, the primary authors of selected studies were contacted for
82 additional information and data.

83 84 **Heterogeneity and risk of bias**

85 For all included studies, methodologic quality was assessed by two
86 authors independently, using the Cochrane risk of bias tool.²⁴ We resolved
87 any disagreement by discussion and, if necessary, consultation with the
88 other authors. Heterogeneity was assessed using the Chi² test and I²
89 statistic, with the level of significance for the Chi² test being set at P = 0.1.²⁵
90 We interpreted values of I² as follows: might not be important (0% to 40%);
91 may represent moderate heterogeneity (30% to 60%); may represent
92 substantial heterogeneity (50% to 90%); and may represent considerable
93 heterogeneity (75% to 100%).

94 95 **Meta-analyses**

96
97 Mean differences with 95% confidence intervals were calculated
98 for continuous data using RevMan (Review Manager; RevMan). When
99 studies used different ways of measuring a continuous outcome
100 standardised mean differences and 95% confidence intervals were
101 calculated. Due to substantial clinical and statistically significant
102 heterogeneity a random-effects model, again with 95% confidence intervals,
103 was employed.

104 105 **Subgroup analyses**

106

107 Subgroup analyses were performed in RevMan. Subgroup analyses
108 included the timing of anti-oxidant administration (pre-exercise versus
109 post-exercise), type of exercise (mechanically induced damage versus
110 whole body aerobic exercise), and funding source (trials funded by food
111 company or provider of antioxidant supplements versus those not funded
112 by food company or provider of antioxidant supplements).

113

114 Results

115 116 Study Characteristics

117
118 We completed the search in February 2017 and 1558 records from
119 the following databases were screened: Cochrane Bone, Joint and Muscle
120 Trauma Group Specialised Register (25 records), CENTRAL (194),MEDLINE
121 (302), Embase (476), SPORTDiscus (117), ClinicalTrials.gov (162) and the
122 WHO International Clinical Trials Registry Platform (282). We also identified
123 12 potentially eligible studies from ongoing searches and through
124 contacting experts in the field. The search resulted in the identification of
125 128 potentially eligible studies, for which we obtained full reports. Upon
126 study selection, we included 50 and excluded 77.

127
128 The 50 trials included in this systematic review had a total of 1089
129 participants with 901 participants in the parallel-group trials (range 7 to 54)
130 and 188 participants in the cross-over trials (range 8 to 24). All 50 studies
131 were randomised controlled trials; no quasi-randomised controlled trials
132 met the inclusion criteria. Thirty-eight trials (with a total of 901
133 participants) employed a parallel design.^{21,22,26-59} The other 12 trials (with a
134 total of 188 participants) employed a cross-over design.⁶⁰⁻⁷¹

135
136 Seven trials were designed to produce DOMS under field-based
137 conditions,^{22,34,43-45,63} and the other 43 studies were designed to produce
138 DOMS under laboratory-based conditions. In all trials, an antioxidant
139 supplement was compared with a placebo. Thirteen trials used antioxidants
140 from a whole natural food source,^{22,28,29,40,43,45,50,61,63,64,67,70,71} 19 used an

141 antioxidant extract or mixed
142 antioxidants,^{26,31,34,36,37,39,41,42,44,47,48,51,52,54,60,65,66,68} and 18 provided either
143 vitamin C or vitamin E or both together.^{21,27,30,32,33,35,38,46,49,53,55,57-59,62,69,72,73}
144 All studies used a placebo either as a powder, capsule or drink; however,
145 three studies did not provide details of what the placebo comprised.^{46,49,60}
146 No trials compared high-dose versus low-dose antioxidant supplements,
147 where the low-dose supplementation is within normal or recommended
148 levels for the antioxidant involved.

149
150 There was a large variation across the studies regarding the
151 duration of supplementation: the shortest period was under one day^{68,69}
152 and the longest period was 91 days.³⁹ Although the form of supplement
153 was varied, including capsules, powders and drinks, every study used an
154 antioxidant dosage higher than the recommended daily amount. Every
155 study required the participant to ingest the supplement orally either once
156 daily or up to three times per day. Supplementation was taken before, the
157 day of and after exercise for up to several days in all the studies except for
158 three studies where supplements were post-exercise only.^{65,67,74}

160 **Funding**

161
162 In all, 21 studies were industry funded either by a food company or
163 a provider of antioxidant supplements.^{26-29,31,32,39,41,43,47,50,52,58,60,61,67-71,73} Of
164 the 28 other studies reporting on funding, 15 declared “none” in their
165 report;^{21,30,33-36,40,44,46,49,53,57,59,62} the other 13 referring to various sources of
166 university and public body research funding sources.^{22,37,38,42,45,48,51,54,55,63-66}

167 We were unsuccessful in obtaining information on funding from the only
168 trial that did not report on this.⁵⁶

170 **Risk of Bias**

171 Forty-seven trials (94%) had design features that were deemed to carry a
172 high risk of bias due to random sequence generation (19 trials),<sup>21,22,27,35,37,41-
173 43,46,49,52,56,57,60,61,65,66,70,71</sup> selective reporting (41 trials),<sup>21,22,26-33,35-40,42,46-49,51,53-
174 63,66-73</sup> poorly described allocation concealment (30 trials),<sup>21,22,27,35-
175 37,40,42,43,45-47,49,51-53,56,58-62,64,65,68-73</sup> attrition bias (12 trials),<sup>32,40,42,45,47,52,54,55,60-
176 62,65</sup> and lack of dietary monitoring during the intervention (16 trials),
177 ^{26,29,31,42,46,49,53-55,57,59,63-66,69} potentially limiting the reliability of their findings.

180 **Primary Outcomes**

181 All of the 50 trials included in this review measured muscle
182 soreness, however, there were differences in the types of soreness scales
183 used. Thirty-three trials measured muscle soreness using a 0 to 10 cm (or 0
184 to 100 mm) visual analogue scale (VAS). Of the 17 other trials, seven^{65,75-80}
185 measured soreness using a 1 to 10 cm scale; four trials^{29,45,81,82} used the 0 to
186 20 cm (or 0 to 200 mm) scale; two studies^{38,48} used a 0- to 6-point scale,
187 Herrlinger³⁹ used a 0 to 7 Likert scale, Drobic³⁶ used a 0- to 4-point scale;
188 Cobley³⁴ used a 0 to 12 cm scale and Su⁵⁶ used the Borg CR-10 scale. The
189 Borg CR-10 scale ranges from 0 (no soreness) to 10 (maximal soreness). In
190 the included studies, participants were asked to rate muscle soreness on
191 the soreness scales by either carrying out a squat using body weight, self-
192 palpitation of muscle or based on muscle soreness at rest.

194 Forty-eight studies presented data on muscle soreness at various
195 different time points based on various visual analogue scale (VAS) scores.
196 Results are presented at eight follow-up times after exercise: up to 6 hours,
197 and at 24, 48, 73, 96, 120, 144 and 168 hours.

198
199 Antioxidant supplementation reduced muscle soreness in
200 comparison to the placebo condition when measured up to 6 hours post-
201 exercise (standardised mean difference (SMD) -0.30, 95% confidence
202 interval (CI) -0.56 to -0.04; participants = 525; studies = 21; $I^2 = 53\%$; low-
203 quality evidence); at 24 hours after exercise (SMD -0.13, 95% CI -0.27 to
204 0.00; participants = 936; studies = 41; $I^2 = 5\%$; moderate-quality evidence);
205 at 48 hours after exercise (SMD -0.24, 95% CI -0.42 to -0.07; participants =
206 1047; studies = 45; $I^2 = 47\%$; low quality evidence); and at 72 hours after
207 exercise (SMD -0.19, 95% CI -0.38 to -0.00; participants = 657; studies = 28;
208 $I^2 = 27\%$; moderate-quality evidence). There was little effect of antioxidants
209 on muscle soreness at 96 hours after exercise (SMD -0.05, 95% CI -0.29 to
210 0.19; participants = 436; studies = 17; $I^2 = 31\%$; low-quality evidence). Far
211 fewer trials provided data at five days or subsequently. There was very low-
212 quality evidence of little effect of antioxidants on muscle soreness at 120
213 hours (SMD 0.21, 95% CI -0.26 to 0.69; participants = 128; studies = 4; $I^2 =$
214 39%), at 144 hours (SMD -0.23, 95% CI -1.11 to 0.65; participants = 20;
215 studies = 1) or at 168 hours (SMD -0.04, 95% CI -0.48 to 0.41; participants =
216 80; studies = 4; $I^2 = 0\%$).

217
218 As there was considerable variation in the units used to measure
219 muscle soreness, we rescaled all trials to the 0 to 10 scale at the first five
220 time points in order to explore the actual difference between groups on a

221 standard scale. The results are as follows: up to 6 hours (mean difference
222 (MD) -0.52, 95%CI -0.95 to -0.08; participants = 525; studies = 21; $I^2 = 66\%$);
223 at 24 hours (MD - 0.17, 95% CI -0.42 to 0.07; participants = 936; studies =
224 41; $I^2 = 29\%$); at 48 hours (MD -0.41, 95% CI -0.69 to - 0.12; participants =
225 1047; studies = 45; $I^2 = 64\%$); at 72 hours (MD -0.29, 95% CI -0.59 to 0.02;
226 participants = 657; studies = 28; $I^2 = 27\%$); and at 96 hours (MD-0.03, 95%
227 CI -0.43 to 0.37; participants = 436; studies = 17; $I^2 = 51\%$). This rescaling
228 also allows us to examine whether the antioxidant supplement produces a
229 clinically important difference. For consistency with Bleakley,⁴ we
230 considered 1.4 cm as the minimal important difference (MID) for pain
231 reduction on a 10 cm visual analogue scale; this was based on an estimated
232 MID for musculoskeletal conditions of the shoulder by Tashjian.⁸³ It is
233 notable that all of the upper limits of the 95% CIs of these five analyses are
234 lower than this MID and hence all quantitative differences do not appear to
235 represent person-relevant differences in muscle soreness.

236 237 **Subgroup and sensitivity analyses**

238
239 We performed only a few subgroup and sensitivity analyses. We
240 selected the 24 and 48 hours analyses for subgroup analyses given that
241 these were the categories with the largest number of trials. We did not use
242 the up to 6 hours time period because of the variation in the timing of
243 measurement: i.e. some studies measured this outcome immediately after
244 exercise whereas other studies measured this up to 2 hours or up to 6
245 hours after exercise. A sensitivity analysis exploring the use of the fixed-
246 effect model for all eight follow-up times produced similar results to that of
247 random-effects model. A subgroup analysis could not be performed on

248 timing of administration (i.e. pre-exercise and post-exercise versus post-
249 exercise only) because there were very few trials (one or two studies
250 depending on the time of follow-up) in the post-exercise group. We
251 performed a subgroup analysis on the type of exercise, that is, mechanically
252 induced versus whole body aerobic exercise for the 24 and 48 hour follow-
253 up times. There is no evidence of subgroup differences for muscle soreness
254 for type of exercise at 24 hours ($\text{Chi}^2 = 0.44$, $\text{df} = 1$; $P = 0.51$, $I^2 = 0\%$) or at
255 48 hours ($\text{Chi}^2 = 0.88$, $\text{df} = 1$; $P = 0.35$, $I^2 = 0\%$). Our second subgroup
256 analysis was based on source of funding where we compared studies that
257 were funded by a food company or provider of antioxidant supplements
258 versus studies that there were not. There is no evidence of subgroup
259 differences for muscle soreness according to source of funding at 24 hours
260 ($\text{Chi}^2 = 0.03$, $\text{df} = 1$, $P = 0.87$, $I^2 = 0\%$) or 48 hours ($\text{Chi}^2 = 0.10$, $\text{df} = 1$, $P =$
261 0.875 $I^2 = 0\%$); no information on funding was available for Su.⁵⁶

262
263 We conducted a sensitivity analysis testing trials at unclear risk of
264 bias, relating to random sequence generation, allocation concealment or
265 both, which included 19 trials.^{22,26,28-34,38,39,44,48,50,54,55,63,67,68} This analysis
266 made little difference to the overall effect at either 24 hours post-exercise
267 (SMD -0.10, 95% CI -0.37 to 0.17; participants = 280; studies = 14; $I^2 = 19\%$)
268 or at 48 hours (SMD -0.31, 95% CI -0.66 to 0.04; participants = 327; studies
269 = 16; $I^2 = 57\%$).

271 **Subjective Recovery**

272 No study measured subjective recovery (return to previous activities
273 without signs or symptoms).

274

Adverse effects

Nine studies^{34,41,43-45,50,52,64,65} reporting on a total of 216 participants, reported on this outcome (very low-quality evidence). One study reported that all six participants in the NAC (N-acetylcysteine) supplementation group had diarrhoea, which was mild in five participants and severe diarrhoea in one.³⁴ The same study reported mild indigestion in four participants (67%) in the NAC group and one of six participants in the placebo group. Another study⁴³ reported that tart cherry juice caused mild gastrointestinal distress in one of 26 participants taking the antioxidant supplement. Seven studies reported no adverse effects of taking the antioxidant supplementation.^{41,44,45,50,52,64,65} The remaining 41 studies failed to report adverse effects.

289 Discussion

290 This review examined the effectiveness of antioxidants for
291 preventing and treating muscle soreness after exercise. Fifty randomised
292 placebo-controlled studies were included, 12 of which used a crossover
293 design. The 50 studies involved a total of 1089 participants (961 male; 128
294 female; age range 16 to 55 years). The studies were heterogeneous,
295 including the timing (pre-exercise or post exercise), frequency, dose or
296 duration, and type of antioxidant supplementation, and the type of
297 preceding delayed onset muscle soreness (DOMS)-producing exercise. All
298 studies used an antioxidant dosage higher than the recommended daily
299 amount. No studies compared high-dose versus low-dose, where the low-
300 dose supplementation was within normal or recommended levels for the
301 antioxidant involved.

302
303 Pooled standardised mean difference (SMD) results for muscle
304 soreness indicated a small difference in favour of antioxidant
305 supplementation after DOMS-inducing exercise at all main follow ups (up to
306 6 hours; low-quality evidence, at 24 hours; moderate-quality evidence, at
307 48 hours; low-quality evidence, at 72 hours; moderate- quality evidence, at
308 96 hours; low-quality evidence. When, however, we rescaled all the trial
309 results to the 0 to 10 cm scale in order to compare the actual difference
310 between groups, we found that the 95% confidence intervals (CIs) for all
311 five follow up times were all below 1.0 cm, and thus all below the minimal
312 important difference of 1.4 cm that we used in this review. Thus, all
313 statistical differences in DOMS favouring antioxidant supplementation were
314 unlikely to equate to meaningful or important differences in practice.

316 Neither of our subgroup analyses to examine for differences in
317 effect according to type of DOMS-inducing exercise (mechanical versus
318 whole body aerobic) or according to funding source confirmed subgroup
319 differences. Sensitivity analyses to test the selection of the statistical model
320 for pooling (fixed-effect instead of random effects) and the exclusion of
321 cross-over studies all showed similar results to the main analyses. None of
322 the 50 studies reported on subjective recovery (return to previous activities
323 without signs or symptoms). Only nine studies (216 participants) reported
324 on adverse effects, with actual events reported in two studies. One study³⁴
325 (12 participants) reported that all six participants in the NAC (N-
326 acetylcysteine supplementation group had diarrhoea, which was mild in
327 five participants and severe in one. The same study³⁴ reported mild
328 indigestion in four participants (67%) in the NAC group and one of six
329 participants in the placebo group. It should be noted that NAC
330 supplementation is usually prescribed and it has been found to cause
331 uncomfortable side effects including nausea and diarrhoea in other studies.
332 Another study⁴³ reported that tart cherry juice caused mild gastrointestinal
333 distress in one of 26 participants taking the antioxidant supplement. The
334 other seven studies reported no adverse effects of taking the antioxidant
335 supplementation; this included 10 participants having NAC
336 supplementation in one study. Overall, the available evidence for adverse
337 events is very low-quality.

338
339 The majority of the 1089 participants included in this review were
340 male (961; 88.2%) and so arguably the findings of the review are mainly
341 applicable to males but there is no biological basis for why antioxidants
342 should have a different effect in the two sexes. These sex differences are

343 typical of what is observed in the athletic recovery literature.^{3,4,7} More
344 noteworthy is that no data from highly-trained elite athletes were included
345 in the analyses; the data pertaining to nine elite athletes tested in
346 McCormick⁶³ were not included in the meta-analyses because the exercise
347 paradigm was completely different to all the other studies included in this
348 review. As the majority of the participants were either college students or
349 relatively young and active, these findings cannot be generalised in the elite
350 athlete population who have a different physiological and training status.
351 Some reservations in terms of applicability also apply to older individuals
352 due to their anatomical and physiological characteristics as there were no
353 older participants included in this review (age range of participants: 16 to
354 55 years).

355
356 We assessed the quality of evidence using the GRADE framework,
357 which combines considerations of risk of bias, indirectness, inconsistency
358 (heterogeneity), imprecision and publication bias. We downgraded all
359 outcomes one level for serious risk of bias, due mainly to selective
360 reporting bias (the majority of the trials failed to report on adverse effects)
361 and, to a lesser degree, attrition biases. We did not downgrade for
362 indirectness in relation to muscle soreness. We downgraded two outcomes
363 for serious inconsistency reflecting heterogeneity that could not be traced
364 to the inclusion of just one outlier trial. Pooled evidence did not support
365 downgrading for imprecision. Our tests for publication bias did not reveal a
366 serious concern, although all were small studies. Thus, we did not
367 downgrade for publication bias. We concluded that the quality of the
368 evidence ranged from moderate to very low.

369

370 It is important to acknowledge some important limitations of this
371 review. Firstly, data from 14 studies^{21,27,35,37,42,47,52,56,60,61,65,67,70,71} were
372 extracted from graphs using Graphclick 2010 Arizona (version 3.0.2, 2010)
373 because the authors did not respond to several emails requested mean and
374 SD data. Whilst this is not ideal, we tried to minimise error by having two
375 review authors (MR and DR) independently extract the data, with any
376 discrepancies resolved by consultation with the third and fourth authors
377 (HS and JC). Secondly, our inclusion of cross-over studies and our analysis of
378 their data as if from a parallel group trial, thus without adjustment for the
379 cross-over design, are other potential sources of bias. With one exception,
380 the cross-over studies included in this review used a washout period of two
381 to six weeks, which is sufficient to allow the muscles to recover. The
382 exception⁶⁰ used a washout period of only five days between treatments
383 and therefore carries some risk of a carry-over effect; sensitivity analysis to
384 check on the effect of excluding the data from this trial did not result in
385 important changes. Further sensitivity analyses checking the effects of
386 excluding the cross-over trials from the muscle soreness analyses showed
387 that our inclusion and handling of the cross-over studies did not have an
388 important impact on the review results.

391 **Conclusions**

393 There is moderate- to low-quality evidence that antioxidant
394 supplementation does not result in a clinically relevant reduction of DOMS
395 after exercise at any of the five follow-up times assessed (up to 6 hours and
396 at 24, 48, 72 and 96 hours after exercise. There is no evidence available on

397 subjective recovery and only limited evidence on adverse effects of taking
398 antioxidant supplements. Some antioxidant supplements such as N-
399 acetylcysteine may cause unwanted side effects including gastrointestinal
400 discomfort and diarrhoea. Thus, taking antioxidants supplements and
401 antioxidant-enriched foods is not an effective strategy to reduce DOMS
402 after exercise.

403

What is already known?

Taking antioxidants supplements to reduce muscle soreness is a common strategy used by recreational and elite athletes. However, little is known about how effective antioxidants are at reducing delayed onset muscle soreness.

What are the new findings?

- There is moderate to low-quality evidence that high dose antioxidant supplementation does not result in a clinically relevant reduction of muscle soreness after exercise at up to 6 hours or at 24, 48, 72 and 96 hours after exercise.
- There is no evidence available on subjective recovery and only limited evidence on the adverse effects of taking antioxidant supplements.
- The findings of, and messages from, this review provide an opportunity for researchers and other stakeholders to come together and consider what are the priorities, and underlying justifications, for future research in this area.

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408 References

- 409 1. Cheung K, Hume PA, Maxwell L. Delayed onset muscle soreness. *Sports*
410 *Medicine*. 2003;33(2):145-164.
- 411 2. Armstrong R. Mechanisms of exercise-induced delayed onset muscular
412 soreness: A brief review. *Med Sci Sports Exerc*. 1984;16(6):529-538.
- 413 3. Bieuzen F, Bleakley CM, Costello JT. Contrast water therapy and exercise
414 induced muscle damage: A systematic review and meta-analysis. *PLoS One*.
415 2013;8(4):e62356.
- 416 4. Bleakley C, McDonough S, Gardner E, et al. Cold-water immersion
417 (cryotherapy) for preventing and treating muscle soreness after exercise.
418 *Sao Paulo medical journal*. 2012;130(5):348-348.
- 419 5. Byrnes W, Clarkson P. Delayed onset muscle soreness and training. *Clin*
420 *Sports Med*. 1986;5(3):605-614.
- 421 6. Cleak M, Eston R. Delayed onset muscle soreness: Mechanisms and
422 management. *J Sports Sci*. 1992;10(4):325-341.
- 423 7. Costello JT, Baker PR, Minett GM, Bieuzen F, Stewart IB, Bleakley C.
424 Whole-body cryotherapy (extreme cold air exposure) for preventing and

- 425 treating muscle soreness after exercise in adults. *The Cochrane Library*.
426 2015.
- 427 8. Asmussen E. Positive and negative muscular work. *Acta Physiol Scand*.
428 1953;28(4):364-382.
- 429 9. Smith LL. Acute inflammation: The underlying mechanism in delayed
430 onset muscle soreness? *Med Sci Sports Exerc*. 1991;23(5):542-551.
- 431 10. De Vries HA. Quantitative electromyographic investigation of the spasm
432 theory of muscle pain. *Ins.Counsel J*. 1967;34:455.
- 433 11. Hough T. Ergographic studies in muscular fatigue and soreness. *J Boston*
434 *Soc Med Sci*. 1900;5(3):81-92.
- 435 12. Weinstock C, König D, Harnischmacher R, Keul J, Berg A, Northoff H.
436 Effect of exhaustive exercise stress on the cytokine response. *Med Sci*
437 *Sports Exerc*. 1997;29(3):345-354.
- 438 13. Davies C, BAKNES C. Negative (eccentric) work. II. physiological
439 responses to walking uphill and downhill on a motor-driven treadmill.
440 *Ergonomics*. 1972;15(2):121-131.

- 441 14. Maughan RJ, Donnelly AE, Gleeson M, Whiting PH, Walker KA, Clough PJ.
442 Delayed-onset muscle damage and lipid peroxidation in man after a
443 downhill run. *Muscle Nerve*. 1989;12(4):332-336.
- 444 15. Margaritelis NV, Cobley JN, Paschalis V, et al. Principles for integrating
445 reactive species into in vivo biological processes: Examples from exercise
446 physiology. *Cell Signal*. 2016;28(4):256-271.
- 447 16. Close GL, Ashton T, McArdle A, Maclaren DP. The emerging role of free
448 radicals in delayed onset muscle soreness and contraction-induced muscle
449 injury. *Comparative Biochemistry and Physiology Part A: Molecular &*
450 *Integrative Physiology*. 2005;142(3):257-266.
- 451 17. Powers SK, Jackson MJ. Exercise-induced oxidative stress: Cellular
452 mechanisms and impact on muscle force production. *Physiol Rev*.
453 2008;88(4):1243-1276.
- 454 18. Ramel A, Wagner K, Elmadfa I. Plasma antioxidants and lipid oxidation
455 after submaximal resistance exercise in men. *Eur J Nutr*. 2004;43(1):2-6.

- 456 19. Witt EH, Reznick AZ, Viguie CA, Starke-Reed P, Packer L. Exercise,
457 oxidative damage and effects of antioxidant manipulation. *J Nutr.*
458 1992;122(suppl_3):766-773.
- 459 20. Tsai K, Hsu T, Hsu K, et al. Oxidative DNA damage in human peripheral
460 leukocytes induced by massive aerobic exercise. *Free Radical Biology and*
461 *Medicine.* 2001;31(11):1465-1472.
- 462 21. Bryer S, Goldfarb AH. Effect of high dose vitamin C supplementation on
463 muscle soreness, damage, function, and oxidative stress to eccentric
464 exercise. *Int J Sport Nutr Exerc Metab.* 2006;16(3):270-280.
- 465 22. Howatson G, McHugh M, Hill J, et al. Influence of tart cherry juice on
466 indices of recovery following marathon running. *Scand J Med Sci Sports.*
467 2010;20(6):843-852.
- 468 23. Mastaloudis A, Traber MG, Carstensen K, Widrick JJ. Antioxidants did
469 not prevent muscle damage in response to an ultramarathon run. *Med Sci*
470 *Sports Exerc.* 2006;38(1):72-80.

- 471 24. Higgins J, Altman DG. Assessing risk of bias in included studies.
472 *Cochrane handbook for systematic reviews of interventions: Cochrane book*
473 *series*. 2008:187-241.
- 474 25. Deeks JJ, Higgins J, Altman DG. Analysing data and undertaking meta-
475 analyses. *Cochrane handbook for systematic reviews of interventions:*
476 *Cochrane book series*. 2008:243-296.
- 477 26. Bailey DM, Williams C, Betts JA, Thompson D, Hurst TL. Oxidative stress,
478 inflammation and recovery of muscle function after damaging exercise:
479 Effect of 6-week mixed antioxidant supplementation. *Eur J Appl Physiol*.
480 2011;111(6):925-936.
- 481 27. Beaton LJ, Allan DA, Tarnopolsky MA, Tiidus PM, Phillips SM.
482 Contraction-induced muscle damage is unaffected by vitamin E
483 supplementation. *Med Sci Sports Exerc*. 2002;34(5):798-805.
- 484 28. Bell PG, Walshe IH, Davison GW, Stevenson EJ, Howatson G. Recovery
485 facilitation with montmorency cherries following high-intensity,
486 metabolically challenging exercise. *Applied Physiology, Nutrition, and*
487 *Metabolism*. 2014;40(4):414-423.

- 488 29. Bell PG, Stevenson E, Davison GW, Howatson G. The effects of
489 montmorency tart cherry concentrate supplementation on recovery
490 following prolonged, intermittent exercise. *Nutrients*. 2016;8(7):441.
- 491 30. Bloomer RJ. Effects of antioxidant therapy in women exposed to
492 eccentric exercise. *Int J Sport Nutr Exerc Metab*. 2004;14(4):377-388.
- 493 31. Bloomer RJ, Fry A, Schilling B, Chiu L, Hori N, Weiss L. Astaxanthin
494 supplementation does not attenuate muscle injury following eccentric
495 exercise in resistance-trained men. *Int J Sport Nutr Exerc Metab*.
496 2005;15(4):401-412.
- 497 32. Bloomer RJ, Falvo MJ, Schilling BK, Smith WA. Prior exercise and
498 antioxidant supplementation: Effect on oxidative stress and muscle injury.
499 *Journal of the International Society of Sports Nutrition*. 2007;4(1):9.
- 500 33. Close GL, Ashton T, Cable T, et al. Ascorbic acid supplementation does
501 not attenuate post-exercise muscle soreness following muscle-damaging
502 exercise but may delay the recovery process. *Br J Nutr*. 2006;95(5):976-981.
- 503 34. Cobley JN, McGlory C, Morton JP, Close GL. N-acetylcysteine's
504 attenuation of fatigue after repeated bouts of intermittent exercise:

- 505 Practical implications for tournament situations. *Int J Sport Nutr Exerc*
506 *Metab.* 2011;21(6):451-461.
- 507 35. Connolly D, Lauzon C, Agnew J, Dunn M, Reed B. The effects of vitamin
508 C supplementation on symptoms of delayed onset muscle soreness. *J*
509 *Sports Med Phys Fitness.* 2006;46(3):462.
- 510 36. Drobic F, Riera J, Appendino G, et al. Reduction of delayed onset
511 muscle soreness by a novel curcumin delivery system (meriva®): A
512 randomised, placebo-controlled trial. *Journal of the International Society of*
513 *Sports Nutrition.* 2014;11(1):31.
- 514 37. Goldfarb AH, Garten RS, Cho C, Chee PD, Chambers LA. Effects of a
515 fruit/berry/vegetable supplement on muscle function and oxidative stress.
516 *Med Sci Sports Exerc.* 2011;43(3):501-508.
- 517 38. He F, Hockemeyer J, Sedlock D. Does combined antioxidant vitamin
518 supplementation blunt repeated bout effect? *Int J Sports Med.*
519 2015;36(05):407-413.

- 520 39. Herrlinger KA, Chirouzes DM, Ceddia MA. Supplementation with a
521 polyphenolic blend improves post-exercise strength recovery and muscle
522 soreness. *Food & nutrition research*. 2015;59(1):30034.
- 523 40. Hutchison AT, Flieller EB, Dillon KJ, Leverett BD. Black currant nectar
524 reduces muscle damage and inflammation following a bout of high-
525 intensity eccentric contractions. *Journal of dietary supplements*.
526 2016;13(1):1-15.
- 527 41. Kerksick CM, Kreider RB, Willoughby DS. Intramuscular adaptations to
528 eccentric exercise and antioxidant supplementation. *Amino Acids*.
529 2010;39(1):219-232.
- 530 42. Krotkiewski M, Brzezinska Z, Liu B, Grimby G, Palm S. Prevention of
531 muscle soreness by pretreatment with antioxidants. *Scand J Med Sci Sports*.
532 1994;4(3):191-199.
- 533 43. Kuehl KS, Perrier ET, Elliot DL, Chesnutt JC. Efficacy of tart cherry juice in
534 reducing muscle pain during running: A randomized controlled trial. *Journal*
535 *of the International Society of Sports Nutrition*. 2010;7(1):17.

536 44. Laupheimer MW, Perry M, Benton S, Malliaras P, Maffulli N. Resveratrol
537 exerts no effect on inflammatory response and delayed onset muscle
538 soreness after a marathon in male athletes.: A randomised, double-blind,
539 placebo-controlled pilot feasibility study. *Transl Med UniSa*. 2014;10:38-42.

540 45. Lynn A, Garner S, Nelson N, Simper T, Hall A, Ranchordas M. Effect of
541 bilberry juice on muscle damage and inflammation in runners completing a
542 half marathon. *Proc Nutr Soc*. 2015;74(OCE5).

543 46. McBRIDE JM, Kraemer WJ, Triplett-McBride T, Sebastianelli W. Effect of
544 resistance exercise on free radical production. *Med Sci Sports Exerc*.
545 1998;30(1):67-72.

546 47. McFarlin BK, Venable AS, Henning AL, et al. Reduced inflammatory and
547 muscle damage biomarkers following oral supplementation with
548 bioavailable curcumin. *BBA clinical*. 2016;5:72-78.

549 48. Meamarbashi A, Abedini F. Preventive effects of purslane extract on
550 delayed onset muscle soreness induced by one session bench-stepping
551 exercise. *Isokinetics Exerc Sci*. 2011;19(3):199-206.

- 552 49. Nie J, Lin H. Effects of vitamin C supplementation on recovery from
553 eccentric exercise-induced muscle soreness and damage in junior athletes.
554 *J Exerc Sci Fit.* 2004;2(2):94-98.
- 555 50. O'Connor PJ, Carvalho AL, Freese EC, Cureton KJ. Grape consumption's
556 effects on fitness, muscle injury, mood, and perceived health. *Int J Sport*
557 *Nutr Exerc Metab.* 2013;23(1):57-64.
- 558 51. O'Fallon KS, Kaushik D, Michniak-Kohn B, Dunne CP, Zambraski EJ,
559 Clarkson PM. Effects of quercetin supplementation on markers of muscle
560 damage and inflammation after eccentric exercise. *Int J Sport Nutr Exerc*
561 *Metab.* 2012;22(6):430-437.
- 562 52. Phillips T, Childs AC, Dreon DM, Phinney S, Leeuwenburgh C. A dietary
563 supplement attenuates IL-6 and CRP after eccentric exercise in untrained
564 males. *Med Sci Sports Exerc.* 2003;35(12):2032-2037.
- 565 53. Shafat A, Butler P, Jensen R, Donnelly A. Effects of dietary
566 supplementation with vitamins C and E on muscle function during and after
567 eccentric contractions in humans. *Eur J Appl Physiol.* 2004;93(1-2):196-202.

- 568 54. Silva LA, Silveira PC, Pinho CA, Tuon T, Pizzol FD, Pinho RA. N-
569 acetylcysteine supplementation and oxidative damage and inflammatory
570 response after eccentric exercise. *Int J Sport Nutr Exerc Metab.*
571 2008;18(4):379-388.
- 572 55. Silva LA, Pinho CA, Silveira PC, et al. Vitamin E supplementation
573 decreases muscular and oxidative damage but not inflammatory response
574 induced by eccentric contraction. *The Journal of Physiological Sciences.*
575 2010;60(1):51.
- 576 56. Su Q, Tian Y, Zhang J, Zhang H. Effects of allicin supplementation on
577 plasma markers of exercise-induced muscle damage, IL-6 and antioxidant
578 capacity. *Eur J Appl Physiol.* 2008;103(3):275.
- 579 57. Theodorou AA, Nikolaidis MG, Paschalis V, et al. No effect of antioxidant
580 supplementation on muscle performance and blood redox status
581 adaptations to eccentric training—. *Am J Clin Nutr.* 2011;93(6):1373-1383.
- 582 58. Thompson D, Williams C, McGregor SJ, et al. Prolonged vitamin C
583 supplementation and recovery from demanding exercise. *Int J Sport Nutr*
584 *Exerc Metab.* 2001;11(4):466-481.

- 585 59. Thompson D, Bailey D, Hill J, Hurst T, Powell J, Williams C. Prolonged
586 vitamin C supplementation and recovery from eccentric exercise. *Eur J Appl*
587 *Physiol.* 2004;92(1-2):133-138.
- 588 60. Arent SM, Senso M, Golem DL, McKeever KH. The effects of theaflavin-
589 enriched black tea extract on muscle soreness, oxidative stress,
590 inflammation, and endocrine responses to acute anaerobic interval
591 training: A randomized, double-blind, crossover study. *Journal of the*
592 *International Society of Sports Nutrition.* 2010;7(1):11.
- 593 61. Connolly DA, McHugh MP, Padilla-Zakour OI, Carlson L, Sayers SP.
594 Efficacy of a tart cherry juice blend in preventing the symptoms of muscle
595 damage. *Br J Sports Med.* 2006;40(8):679-83; discussion 683.
- 596 62. Kaminski M, Boal R. An effect of ascorbic acid on delayed-onset muscle
597 soreness. *Pain.* 1992;50(3):317-321.
- 598 63. McCormick R, Peeling P, Binnie M, Dawson B, Sim M. Effect of tart
599 cherry juice on recovery and next day performance in well-trained water
600 polo players. *Journal of the International Society of Sports Nutrition.*
601 2016;13(1):41.

- 602 64. McLeay Y, Barnes MJ, Mundel T, Hurst SM, Hurst RD, Stannard SR.
603 Effect of new zealand blueberry consumption on recovery from eccentric
604 exercise-induced muscle damage. *Journal of the International Society of*
605 *Sports Nutrition*. 2012;9(1):19.
- 606 65. Michailidis Y, Karagounis LG, Terzis G, et al. Thiol-based antioxidant
607 supplementation alters human skeletal muscle signaling and attenuates its
608 inflammatory response and recovery after intense eccentric exercise—. *Am J*
609 *Clin Nutr*. 2013;98(1):233-245.
- 610 66. Nicol LM, Rowlands DS, Fazakerly R, Kellett J. Curcumin
611 supplementation likely attenuates delayed onset muscle soreness (DOMS).
612 *Eur J Appl Physiol*. 2015;115(8):1769-1777.
- 613 67. Peschek K, Pritchett R, Bergman E, Pritchett K. The effects of acute post
614 exercise consumption of two cocoa-based beverages with varying flavanol
615 content on indices of muscle recovery following downhill treadmill running.
616 *Nutrients*. 2013;6(1):50-62.
- 617 68. Tanabe Y, Maeda S, Akazawa N, et al. Attenuation of indirect markers of
618 eccentric exercise-induced muscle damage by curcumin. *Eur J Appl Physiol*.
619 2015;115(9):1949-1957.

- 620 69. Thompson D, Williams C, Kingsley M, et al. Muscle soreness and
621 damage parameters after prolonged intermittent shuttle-running following
622 acute vitamin C supplementation. *Int J Sports Med.* 2001;22(01):68-75.
- 623 70. Trombold JR, Barnes JN, Critchley L, Coyle EF. Ellagitannin consumption
624 improves strength recovery 2–3 d after eccentric exercise. *Med Sci Sports
625 Exerc.* 2010;42(3):493-498.
- 626 71. Trombold JR, Reinfeld AS, Casler JR, Coyle EF. The effect of
627 pomegranate juice supplementation on strength and soreness after
628 eccentric exercise. *J Strength Cond Res.* 2011;25(7):1782-1788.
- 629 72. Avery NG, Kaiser JL, Sharman MJ, et al. Effects of vitamin E
630 supplementation on recovery from repeated bouts of resistance exercise. *J
631 Strength Cond Res.* 2003;17(4):801-809.
- 632 73. Thompson D, Williams C, Garcia-Roves P, McGregor S, McArdle F,
633 Jackson M. Post-exercise vitamin C supplementation and recovery from
634 demanding exercise. *Eur J Appl Physiol.* 2003;89(3-4):393-400.

- 635 74. Thompson D, Williams C, Garcia-Roves P, McGregor SJ, McArdle F,
636 Jackson MJ. Post-exercise vitamin C supplementation and recovery from
637 demanding exercise. *Eur J Appl Physiol*. 2003;89(3-4):393-400.
- 638 75. Bryer SC, Goldfarb AH. Effect of high dose vitamin C supplementation
639 on muscle soreness, damage, function, and oxidative stress to eccentric
640 exercise. *Int J Sport Nutr Exerc Metab*. 2006;16(3):270-280.
- 641 76. Bailey DM, Williams C, Betts JA, Thompson D, Hurst TL. Oxidative stress,
642 inflammation and recovery of muscle function after damaging exercise:
643 Effect of 6-week mixed antioxidant supplementation. *Eur J Appl Physiol*.
644 2011;111(6):925-936.
- 645 77. Goldfarb AH, Garten RS, Cho C, Chee PD, Chambers LA. Effects of a
646 fruit/berry/vegetable supplement on muscle function and oxidative stress.
647 *Med Sci Sports Exerc*. 2011;43(3):501-508.
- 648 78. Kaminski M, Boal R. An effect of ascorbic acid on delayed-onset muscle
649 soreness. *Pain*. 1992;50(3):317-321.

- 650 79. Thompson D, Williams C, Kingsley M, et al. Muscle soreness and
651 damage parameters after prolonged intermittent shuttle-running following
652 acute vitamin C supplementation. *Int J Sports Med.* 2001;22(1):68-75.
- 653 80. Thompson D, Williams C, Garcia-Roves P, McGregor SJ, McArdle F,
654 Jackson MJ. Post-exercise vitamin C supplementation and recovery from
655 demanding exercise. *Eur J Appl Physiol.* 2003;89(3-4):393-400.
- 656 81. Bell PG, Stevenson E, Davison GW, Howatson G. The effects of
657 montmorency tart cherry concentrate supplementation on recovery
658 following prolonged, intermittent exercise. *Nutrients.* 2016;8(7):441.
- 659 82. Howatson G, Milak A. Exercise-induced muscle damage following a bout
660 of sport specific repeated sprints. *J Strength Cond Res.* 2009;23(8):2419-
661 2424.
- 662 83. Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically
663 important differences (MCID) and patient acceptable symptomatic state
664 (PASS) for visual analog scales (VAS) measuring pain in patients treated for
665 rotator cuff disease. *J Shoulder Elbow Surg.* 2009;18(6):927-932.
- 666

667 Contributorship

668 Mayur Ranchordas identified the research idea for the review, wrote the
669 protocol, extracted the data, wrote the review and is the
670 guarantor.

671 David Rogerson assisted with drafting the protocol and data extraction.

672 Hora Soltani provided feedback on the draft protocol and review.

673 Joseph Costello assisted with data analysis and drafted the final review.

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