

Effects of Dietary Supplements on Adaptations to Endurance Training

Short title/running head: Supplements and Training Adaptations

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Abstract

Endurance training leads to a variety of adaptations at the cellular and systemic levels that serve to minimise disruptions in whole-body homeostasis caused by exercise. These adaptations are differentially affected by training volume, training intensity, and training status, as well as by nutritional choices that can enhance or impair the response to training. A variety of supplements have been studied in the context of acute performance enhancement, but the effects of continued supplementation concurrent to endurance training programs are less well characterised. For example, supplements such as sodium bicarbonate and beta-alanine can improve endurance performance and possibly training adaptations during endurance training by affecting buffering capacity and/or allowing an increased training intensity, while antioxidants such as vitamin C and vitamin E may impair training adaptations by blunting cellular signaling but appear to have little effect on

39 performance outcomes. Additionally, limited data suggest the potential for dietary nitrate
40 (in the form of beetroot juice), creatine, and possibly caffeine, to further enhance endurance
41 training adaptation. Therefore, the objective of this review is to examine the impact of
42 dietary supplements on metabolic and physiological adaptations to endurance training.
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50 **Key Points**

- 51 • Many supplements have been studied in the context of acute performance
52 enhancement, but the effects of continued supplementation concurrent to endurance
53 training programs are less well characterised.
- 54 • Supplements including sodium bicarbonate, beta-alanine, dietary nitrates,
55 antioxidants, caffeine, and creatine have the potential to modify the adaptive
56 response to endurance training (either positively or negatively) by affecting acid-
57 base balance, redox status, oxidant signaling, or cumulative training load, thereby
58 affecting the cellular signaling responses to training.
59

60

61

62 **1. Introduction**

63 Endurance training (repeated sessions of continuous or intermittent exercise performed
64 with the goal of improving endurance performance) leads to metabolic and morphological
65 adaptations at the cellular and systemic levels, which allow submaximal-intensity exercise
66 to be performed with a smaller homeostatic disturbance [1]. These adaptations include
67 increases in maximal oxygen uptake (VO_{2max}), mitochondrial enzyme activity, and
68 mitochondrial protein content, which result in a shift towards greater reliance on fat for fuel,
69 reduced glycolytic flux, decreased lactate accumulation at a given work rate, and tighter
70 control of acid–base balance [1-3].

71
72 Training-induced adaptations are the consequence of repeated stimuli from individual
73 exercise sessions [3], and the accumulation over time of transient, exercise-induced changes
74 in gene expression [4]. Manipulation of training intensity and duration are the primary
75 variables affecting the exercise response [5]. However, dietary intake can also impact
76 adaptations to training by increasing the exercise stimulus and/or enhancing or blunting
77 cellular responses to exercise-induced perturbations (Fig. 1) [6].

78
79 Elite athletes use dietary supplements more than non-elite athletes, with a similar
80 prevalence between men and women [7]. Although the motivations for using these
81 supplements are often not with the goal of improving adaptations to training, the use of
82 dietary supplements represents an under-researched and under-appreciated approach for
83 impacting the adaptive response to endurance training.

84
85 The performance effects of supplements commonly used by endurance athletes, including
86 sodium bicarbonate, β -alanine, and dietary nitrates, has been reviewed [8-13]. However,
87 these supplements are typically considered only in the context of acute performance changes
88 and less is known about how they influence adaptations to training. These supplements have
89 the potential to modify the adaptive response to endurance training (either positively or
90 negatively) by affecting acid-base balance, redox status, reactive oxygen species (ROS)
91 signaling, or cumulative training load, thereby affecting the cellular signaling responses to
92 training (Fig. 2). Some discussion of the effects of supplements on training adaptations has
93 previously been published [14-16], but these were focused on a narrow subset of

94 supplements and did not include creatine or caffeine, or research published over the past
95 five years. Thus, an updated overview of the current literature is warranted. The objective of
96 this review is to examine the impact of common dietary supplements on the metabolic and
97 physiological adaptations to endurance training.

98

99 **2. Buffering Agents**

100 Supplements that act on buffering and pH regulation may affect the training response by
101 allowing an athlete to train harder (increasing the exercise stimulus), and/or impacting
102 important signaling molecules, such as the 5' AMP-activated protein kinase (AMPK), p38
103 mitogen-activated protein kinase (MAPK), and the Ca²⁺/calmodulin-dependent kinase
104 (CaMK) pathways, which are affected by pH [17-19]. For example, an acidic pH decreased
105 the protein content of phosphorylated AMPK in differentiated L6 myotubes [19], cultured
106 fibroblasts [20], and rat cardiomyocytes [21], while an alkaline pH increased phosphorylated
107 AMPK protein content in rat cardiomyocytes [21]. In humans, inducing acidosis with
108 ammonium chloride before a session of interval exercise blunted the post-exercise increases
109 in peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α), citrate synthase
110 (CS), cytochrome C (CYT-C), and *GLUT4* mRNA compared with a placebo [22] (Fig. 3). Blood
111 lactate concentrations are also decreased in acidosis, likely due to the attenuation of
112 glycolytic activity [23]. This may negatively impact training adaptations as lactate signaling
113 can influence mitochondrial biogenesis [24] and the chronic adaptive response to training
114 [25]. An increase in blood pH can increase the rate of muscle glycogen breakdown along with
115 increasing blood lactate levels and H⁺ efflux out of contracting muscles [26, 27]. Increasing
116 blood pH via ingestion of sodium bicarbonate prior to a session of high-intensity exercise

117 increased the expression of *PGC-1 α* mRNA to a greater degree than a placebo [27]. Although
118 acute responses to training do not always correspond with long-term adaptations [28], there
119 is evidence to suggest that supplements that alter pH may affect adaptations to training.

120

121 *2.1 Sodium Bicarbonate*

122 Sodium bicarbonate is typically consumed in a dose of 0.2 to 0.4 grams per kg of bodyweight,
123 divided across one to three servings [16], although serial loading protocols over several days
124 have also been used [29]. This dose should be sufficient to raise bicarbonate concentrations
125 in the blood by 5 to 6 mmol/L and allow small changes in blood pH during sub-maximal
126 exercise, although large interindividual variability in the response to supplementation has
127 been reported [30-32]. Ingestion of sodium bicarbonate before each cycling interval training
128 session (24 sessions over eight weeks) in recreationally-active women resulted in greater
129 improvements in the lactate threshold (26 vs. 15%, $d = 0.5$) and time to fatigue (164 vs 123%,
130 $d = 1.9$) compared with a placebo, even though training volume and intensity was matched
131 between groups (Table 1) [33]. Six weeks of high-intensity interval training (HIIT) (18
132 sessions) by recreationally-active men consuming sodium bicarbonate or a placebo prior to
133 each training session led to greater improvement in relative peak power (20.8 vs. 10.3%, d
134 = 2.1) but no differences in relative mean power on a Wingate test [34], and similar
135 improvements in time to fatigue, maximum power, and lactate threshold power, though only
136 the bicarbonate group had significant increases in CS activity (22.3 vs. 12.6%) [35]. However,
137 four weeks of sodium bicarbonate supplementation in highly-trained male rowers did not
138 provide significant performance benefits compared with a placebo [36]. While favourable
139 trends were observed for 2,000-m power, peak power, and power at the lactate threshold, it

140 is possible that performing only 8 sessions over the 4-week study period and/or the small
141 sample size ($n=6$ per group) was not sufficient to detect significant changes.

142

143 Rats performing HIIT on a treadmill five times per week for five weeks had a 52% longer
144 time to exhaustion ($d = 11.1$), and greater improvements in ADP-stimulated mitochondrial
145 respiration ($d = 1.8$), when consuming sodium bicarbonate before exercise, compared with
146 rats that ingested a placebo prior to exercise [37, 38]. These groups were also matched for
147 total work performed during each training session, further supporting the potential for
148 bicarbonate to improve adaptations to training. Changes in the activity of CS and
149 phosphofructokinase, and sodium bicarbonate cotransporter protein content, were similar
150 to the placebo group [37, 38], although levels of monocarboxylate transporter 4 increased to
151 a greater degree after training with bicarbonate supplementation [38].

152

153 Overall, sodium bicarbonate is unlikely to have an effect on VO_{2max} (which is largely affected
154 by central adaptations [39]), but may affect peripheral adaptations that are influenced by pH
155 such as the lactate threshold, CS activity, and mitochondrial respiration, particularly in
156 untrained participants (Fig. 3). Contrasting results may be due to differences in fitness level,
157 number and intensity of training sessions performed, sex differences, genetics, and sample
158 size. Two studies that showed no differences between groups prescribed HIIT at a
159 percentage of peak power [35, 36], while a study that set training intensity as a percentage
160 of the lactate threshold resulted in improved performance [33].

161

162 Future research should elucidate differences in mitochondrial enzyme content and
163 respiration as a result of sodium bicarbonate ingestion prior to training sessions. Exercise
164 stimuli should be sufficient to alter lactate levels and/or pH compared with a placebo, and
165 should compare both work-matched and time-based (e.g., 4-min intervals at maximal effort)
166 intervals to examine the effects of differences in pH versus differences in total work during
167 training sessions.

168

169 *2.2 Beta-alanine*

170 Beta-alanine is an increasingly popular supplement for athletes due to its ability to delay
171 fatigue during high-intensity exercise. It does this by increasing muscle carnosine content in
172 a dose-dependent manner [40], and improvements in exercise performance have been
173 shown with doses ranging from 3.2 to 6.4 g/day for 4 to 24 weeks [9]. β -alanine has the
174 potential to enhance training adaptations by increasing the ability to sustain exercise at a
175 higher intensity [41], and allowing athletes to better tolerate greater training volumes with
176 decreased subjective feelings of fatigue [42]. As β -alanine is considered primarily effective
177 within 1- to 10-minute time frames [9], endurance athletes who undertake interval training
178 sessions within that duration may benefit from an improved adaptive response to training
179 by accumulating a greater workload during each session. This may be due to a number of
180 inter-related factors including improved pH buffering [43], which can allow a greater
181 reliance on aerobic metabolism and thus reduced accumulation of glycolytic metabolites for
182 the same exercise intensity [44], decreased levels of blood lactate during the recovery from
183 supra-maximal exercise [45], a reduction in oxidative stress due to the antioxidant effects of
184 carnosine that could allow improved recovery between demanding workouts [46-48], an

185 increased threshold for neuromuscular fatigue [41], and/or reduced feelings of fatigue
186 during periods of heavy training [42, 44]. It has also been suggested that increases in calcium
187 sensitivity [49], or in calcium re-uptake [50], may also play a role in the ergogenic effects of
188 β -alanine by helping to slow the decline in muscle performance during fatiguing exercise.
189 From a cell-signaling perspective, β -alanine supplementation may impact mitochondrial
190 biogenesis via increased calcium re-uptake [50] and its downstream effects on AMPK, CaMK,
191 and extracellular-signal-regulated kinases (ERK) 1 and 2 [51], increased expression of
192 peroxisome proliferator-activated receptor (PPAR) β/δ [52], and/or greater lactate signaling
193 [24, 53] (Fig. 2).

194

195 Most studies have investigated the effects of β -alanine on exercise performance, with
196 relatively few studies considering the effects of supplementation on adaptations to training
197 (Table 1). Of the studies that have measured changes in VO_{2peak} after endurance training,
198 none have reported greater improvements from supplementation compared with the
199 placebo groups [53-57]. This finding is similar to sodium bicarbonate and would be expected
200 as buffering agents are more likely to exert their effects in the skeletal muscle rather than
201 through central mechanisms. However, similar increases in cytochrome-c oxidase and β -
202 hydroxyacyl-CoA dehydrogenase (β -HAD) maximal activities were found in active but
203 untrained men taking β -alanine or a placebo during six weeks of Sprint Interval Training
204 (SIT) (three sessions per week) [55], suggesting differences in peripheral adaptations may
205 not be seen when total work performed is the same. This is in contrast to some findings for
206 sodium bicarbonate [33, 34].

207

208 Performance improvements with β -alanine supplementation, compared with a placebo, have
209 been reported for 10-km time-trial running performance (\sim 54 min) following three weeks
210 of run training [58], and cycling time-to-exhaustion at 120% of peak power (\sim 3.5 min)
211 following a five-week SIT program [53] (Table 1). There was also a trend for greater
212 improvement in cycling time-to-exhaustion at 110% of peak power (\sim 23 min) after six
213 weeks of HIIT [57]. In contrast, four to six weeks of interval training in recreationally-active
214 participants taking β -alanine or a placebo resulted in similar improvements for 250-kJ (\sim 20
215 min) time-trial performance [55], average power during a 4-min time-trial [59], power at the
216 ventilatory threshold [54], and critical power during a 3-minute all-out cycling test [56].
217 Considering its established effects on high-intensity exercise performance [9], it is
218 challenging to distinguish the effects of β -alanine on performance from its effects on
219 adaptations to training. However, as shown in Figure 4, there appear to be both independent
220 and additive benefits of SIT and β -alanine supplementation.

221
222 One of the proposed mechanisms for β -alanine to improve training adaptations is an
223 increased training intensity. This was observed in one study that showed improvements
224 [53], while a trend for increased training intensity was seen in another that also showed
225 favorable improvements [57]. Furthermore, there were increased blood lactate levels during
226 sprint intervals with supplementation, compared with a placebo [53, 60]. Although training
227 intensities were not reported in two other studies that showed improvements, they used
228 interval-training protocols that elicited maximal, rather than pre-determined, effort levels
229 [56, 58]. No differences in training intensity were seen in studies that showed no additional
230 improvements from β -alanine either with maximal (30-s) sprint training [55] or sprints at

231 pre-determined work intensities [54, 59, 61]. This suggests greater training adaptations with
232 β -alanine supplementation are less likely to be observed if training intensities are
233 intentionally clamped or the chosen interval prescriptions are outside of the 1 to 10 minute
234 range of exercise where β -alanine exerts its most prominent influence [62]. With typical
235 dosing regimens of 3.2 to 6.4 g/d, at least two weeks of supplementation is needed to elevate
236 muscle carnosine concentrations [40, 63], before potentially exerting beneficial effects on
237 training intensity. Therefore, muscle carnosine loading may be beneficial prior to
238 undertaking an exercise training study.

239

240 *2.3 Summary*

241 The use of sodium bicarbonate (which causes an acute change in blood buffering capacity)
242 or β -alanine (which causes a chronic change in muscle buffering capacity) show potential for
243 allowing greater adaptations to training, though the data are mixed. Contrasting results may
244 be due to differences in training status, training intensity, or the use of interval prescriptions
245 that clamp exercise intensities and/or may fall outside of the optimal duration for the
246 supplement to be effective (e.g. <60 s). Furthermore, responses to sodium bicarbonate
247 appear subject to both intra-[31] and inter-[64] individual variability, at least in untrained
248 participants. Although the performance effects of co-ingesting sodium bicarbonate and β -
249 alanine are unclear [65], several studies have investigated the effects of combined
250 supplementation on training adaptations [66-68]. While a 4-wk loading period of β -alanine
251 supplementation is typically used when studying co-ingestion, in all but one study [61]
252 participant training sessions were not monitored. As discussed, differences in training

253 intensity appear necessary to see beneficial training adaptations with β -alanine
254 supplementation.

255

256 Research using doses that have been shown to increase blood pH or muscle carnosine
257 content should investigate the longer-term effects of sodium bicarbonate and β -alanine
258 supplementation on training capacity to determine if athletes can increase their training
259 volume, which could allow greater training adaptations and, in turn, better performance, as
260 well as the effects of training status on training adaptations. Particularly for β -alanine,
261 interval prescriptions should avoid pre-determined workloads (e.g. 4 min at 90% of peak
262 power), in favor of distance or time-based intervals (e.g. 1-km, or 4-min maximal efforts). If
263 set workloads are required, using a percentage of lactate threshold may be preferable to a
264 percentage of VO_{2peak} . In addition to work completed during each session, measurement of
265 blood lactate concentrations may be useful in determining if changes in lactate levels,
266 compared with a placebo, can be predictive of an augmented training response (Table 2).

267

268 **3. Dietary Nitrate**

269 Dietary nitrate (NO_3^-), commonly supplemented and studied in the form of beetroot juice,
270 has the potential to augment adaptations to endurance training due to its ability to increase
271 plasma levels of nitrite (NO_2^-) and nitric oxide (NO) [69]. It can increase training intensity
272 [70] (and thus total amount of work completed in a workout) by enhancing mitochondrial
273 efficiency [71], reducing the oxygen cost of muscle contraction [72], and increasing
274 contractile force in fast-twitch muscles [73]. Increases in mitochondrial biogenesis (via NO
275 stimulation of guanylate cyclase leading to activation of PGC-1 α) [74], and a shift in muscle

276 fibre type towards a more oxidative phenotype when combined with SIT (via nitric oxide's
277 role in calcineurin-NFAT [nuclear factor of activated T-cells] signaling) have also been
278 reported [75-77], which are possibly related to increases in mitochondrial hydrogen
279 peroxide [78]. However, by reducing the oxygen cost of muscle contraction, thereby reducing
280 the metabolic stress inside the muscle, it is also possible that nitrate supplementation may
281 impair training adaptations via decreased activation of cell-signaling pathways (e.g. AMPK,
282 CaMK, and PGC-1 α) [79].

283

284 The majority of studies showing beneficial effects of supplementation on endurance
285 performance have used doses of 6 to 8 mmol NO₃⁻ taken as a single dose 2 to 3 hours prior
286 to exercise or with a loading period of 5 to 8 days [10], although higher doses (e.g. 8 to 12
287 mmol) may be required for elite athletes [80]. Plasma levels of NO₂⁻, used as a marker of NO
288 availability [81], are increased in a dose-dependent manner but benefits may plateau
289 between 8 and 16 mmol NO₃⁻ [82]. No effects of beetroot juice were observed after six weeks
290 of cycling HIIT when ingesting ~5 mmol NO₃⁻ per day [83], while training studies using 8 to
291 12.8 mmol NO₃⁻ per day have shown benefits [75, 84-86].

292

293 Seven studies have supplemented dietary nitrate while undergoing supervised endurance
294 training for at least three weeks [75, 77, 83-87] (Table 3). Four weeks of SIT combined with
295 beetroot juice supplementation resulted in training-induced improvements in VO_{2peak} of 7.7
296 to 10.7% [85, 75], which were greater than with SIT alone (+5.6%) or after SIT with
297 potassium NO₃⁻ (KNO₃) supplementation (+4.2%) [85]. Time-to-fatigue during high-
298 intensity cycling (power at the gas exchange threshold plus 85% of the difference between

299 that work rate and VO_{2peak}) also improved more with SIT+ beetroot juice (+71%) compared
300 to SIT alone (+47%) and SIT+KNO₃ (+42%) [85]. Greater reductions in blood pressure were
301 observed with SIT+ beetroot juice compared with SIT+KNO₃, a disparity that has also been
302 reported between the ingestion of beetroot juice and NaNO₃ [88] and may be related to the
303 presence of other bioactive compounds found in beetroot juice [89]. Though speculative, the
304 greater decrease in plasma NO₂⁻ observed during exercise with SIT+ beetroot juice compared
305 with SIT+KNO₃ may suggest enhanced NO synthesis during exercise, and is in accordance
306 with observed correlations between the decline in plasma NO₂⁻ and improvements in
307 exercise performance [90]. Two of the training studies used NaNO₃ as the source of nitrate
308 (6.5 and 11 mmol per day), and neither found any additional performance improvements
309 [77, 87]. Further research should examine the effects of supplementation with different
310 dietary nitrate sources on adaptations to endurance training.

311

312 Similar to buffering agents, dietary nitrate works primarily on peripheral metabolism and
313 short-term intake would not be expected to have an appreciable influence on VO_{2peak} . One
314 explanation for the observed improvements in VO_{2peak} may be related to changes in muscle
315 fibre type. The percentage of slow-twitch fibres is directly related to VO_{2peak} and endurance
316 performance [91, 92], and the two studies that showed an additional increase in VO_{2peak} with
317 supplementation also found changes in fibre-type composition [75, 85]. A decreased
318 proportion of type Ix muscle fibres in the vastus lateralis was observed in the nitrate group
319 compared with placebo [75], and there was a greater increase in the proportion of type IIa
320 fibres after both SIT alone (+20%) and SIT+ beetroot juice (+14%), compared with
321 SIT+KNO₃ (non-significant decrease) [85]. It is unclear if these differences suggest that

322 SIT+KNO₃ is not as effective as SIT alone, or if this highlights the variability and/or reliability
323 of fibre-type measures, which are reported to have inter-biopsy coefficient of variations of
324 21.5, 15.4 and 42.0 % for type I, IIa and IIx fibres, respectively [93]. Five weeks of SIT in
325 hypoxia with NaNO₃ supplementation also increased the relative number of type IIa fibres,
326 which was not observed with placebo supplementation in either normoxia or hypoxia,
327 although similar improvements between groups were seen in VO_{2max}, the lactate threshold,
328 and CS activity [77]. This is in accordance with *in vitro* research showing nitrate increased
329 *PGC-1α* gene expression and a switch toward type I and IIa muscle fibres [94].

330

331 Two studies have examined the effects of dietary nitrate on training adaptations one to seven
332 days after stopping supplementation [95, 87]. Twenty-eight days of NO₃⁻ supplementation in
333 recreationally-active participants who maintained their typical exercise habits was followed
334 by exercise testing after one day of placebo or continued nitrate in order to study chronic +
335 acute vs. chronic-only dosing [95]. There was a reduction in the oxygen cost of submaximal
336 cycling even up to 24 h after consuming the final dose of NO₃⁻, which was similar to what was
337 observed after 28 days of supplementation followed by an acute dose of NO₃⁻ prior to testing
338 [95]. There are several potential reasons for this observation, including lasting
339 improvements in mitochondrial [71] or muscle contractile efficiency [72] from chronic
340 supplementation, or that in spite of plasma nitrite concentrations returning to baseline after
341 24 h NO bioavailability remained elevated as a result of stored NO₂⁻ and NO₃⁻ in skeletal
342 muscle [96]. Another study investigated three weeks of high-volume HIIT in recreationally-
343 active participants consuming either ~11 mmol NaNO₃⁻ per day or a placebo, who performed
344 a series of exercise tests two to seven days after the final day of supplementation [87]. Total

345 oxygen consumption decreased by 5% in the supplement group but not the placebo group
346 during a time to exhaustion test at 80% W_{\max} that was performed 4 to 5 days after cessation
347 of supplementation, although no differences were seen between groups for improvements
348 in the time itself or in $VO_{2\text{peak}}$ [87]. Overall, limited data suggest the beneficial effects of NO_3^-
349 supplementation on oxygen consumption during submaximal exercise may continue to be
350 observed for up to 5 days, but mechanisms and the exact time-course of washout remains to
351 be elucidated.

352

353 *3.1 Summary*

354 The limited evidence suggests there may be small but favourable effects of endurance
355 training with nitrate supplementation, which are possibly related to changes in muscle fibre-
356 type. Beetroot juice may be more effective than nitrate salts, though the efficacy of
357 supplementation can be affected by inter-individual variability [97] and environmental
358 conditions [98]. All studies to date have used high-intensity training protocols, as dietary
359 nitrate is particularly effective at augmenting physiological responses in type II fibres [99].
360 Studies using other forms of endurance training are needed to differentiate acute ergogenic
361 benefits from the chronic effects of dietary nitrate on training adaptations. More research is
362 required to determine the role of nitric oxide on mitochondrial biogenesis [74], as well as to
363 investigate differences in the skeletal muscle remodeling responses - particularly between
364 untrained and endurance-trained participants (Table 2).

365

366 **4. Antioxidants**

367 Free radicals are produced during aerobic metabolism and play a role in both exercise-
368 induced fatigue and the adaptive response to exercise [100]. Muscle contractile force is
369 decreased by elevated levels of reactive oxygen and nitrogen species (RONS), largely due to
370 changes in myofibrillar calcium sensitivity [101]. At the same time, RONS generated during
371 exercise act as signaling molecules to increase the production of proteins involved in the
372 skeletal muscle adaptation to exercise such as NO synthase, superoxide dismutase (SOD),
373 and MAP kinases p38, ERK1 and ERK2 (Fig. 2) [102, 103]. For example, RONS, via AMPK
374 activation, can induce PGC-1 α promoter activity and mRNA expression [104]. Due to their
375 effects of reducing RONS, antioxidants have the potential to impair the adaptive responses
376 to RONS-induced stressors and therefore negate favourable training adaptations that would
377 normally occur [105], while also having the potential to improve recovery and acute
378 performance [106-108]. Some antioxidants, including polyphenols, may exert their effects in
379 areas beyond RONS signaling, such as increased mobilisation of fatty acids [109] or sirtuin 1
380 (SIRT1) activation (Fig. 2) [110]. For additional discussion of the effects of antioxidant
381 supplementation on exercise performance the reader is referred to recent reviews [14, 105,
382 111].

383

384 *4.1 Vitamins C and E*

385 Vitamins C and E are antioxidant vitamins with a role in protecting cellular organelles from
386 oxidative damage [112, 113]. No impact on exercise performance outcomes has been
387 observed in human studies when supplementing with vitamins C and/or E during controlled
388 endurance training [114-125] (Table 4). Skeletal muscle adaptations, such as training-
389 induced increases in CS or β -HAD enzyme activity, mRNA or protein levels of cytochrome c

390 oxidase subunit IV (COX-IV), heat shock protein 70, or changes in substrate oxidation, have
391 not been affected by supplementation in healthy participants after 4 to 12 weeks of training
392 [120, 123-126]. In contrast, supplementation with vitamins C and E for 4 to 11 weeks has
393 blunted training-induced increases in COX-IV, PGC-1 α , PGC-1 β , PPAR γ , SOD, and GPx protein
394 compared with a placebo in both untrained and previously-trained participants [122, 127].
395 Animal studies have also shown that 4 to 14 weeks of aerobic training with antioxidant
396 intake blunted training-induced increases in cytochrome oxidase and CS activity,
397 mitochondrial transcription factor A (TFAM), CYT-C, GPx, glutathione reductase, SOD, PGC-
398 1 α , NRF-1, and NRF-2 [118, 128-130], although other research has shown no effect on
399 markers of training adaptations such as mitochondrial respiratory capacity, and CYT-C, COX-
400 I, COX-IV, CS, NRF-1, or PGC-1 α protein content [130-133].

401
402 The reason for these divergent findings, particularly in the animal research, may be due to
403 variations in dosing, exercise protocols, and baseline levels of endogenous antioxidants. The
404 amount of antioxidant provided has varied more than 10-fold [128, 134], exercise type has
405 included both running and swimming, and the duration of training sessions has ranged from
406 30 min to six hours per day [132-134]. Potential redundancies in the adaptation process
407 must also be considered. For example, contracting skeletal muscle activates AMPK via its
408 upstream kinase Ca²⁺/calmodulin-dependent protein kinase kinase (CaMKK) [135], and
409 changes in proteins regulating fat metabolism such as FAT/CD36 are mediated in part by
410 contraction-induced signaling of the ERK1/2 pathway [136]. Thus, many of the common
411 adaptations to endurance training may be observed in the absence of RONS signaling and be
412 minimally influenced by antioxidant supplementation.

413

414 It should also be considered that some effects may be missed due to small sample sizes. For
415 example, the two human studies showing a blunting of training adaptations with antioxidant
416 supplementation also had the largest sample sizes [122, 127]. In contrast, eight weeks of
417 endurance training with or without supplementation had no statistical effect on increases in
418 VO_{2max} , but the vitamin C group (n=5) improved by 10.8% while the group without
419 supplementation (n=9) improved by 22% ($d = -1.0$) [118].

420

421 The effects of vitamins C and E supplementation on markers of oxidative stress have also
422 been variable, with reports of reductions [116], increases [119, 137], and no impact [123,
423 138]. This may be primarily related to methodological issues including the use of assays that
424 are no longer recommended, short half-lives of oxidants being measured, and lack of
425 measurement specificity, making both conducting and interpreting the available research
426 difficult [139-141]. More research is needed before a conclusion can be drawn regarding the
427 impact of vitamins C and E on markers of oxidative stress during endurance training.

428

429 *4.2 Polyphenols*

430 Polyphenols are antioxidants found in plants, with the potential to impact chronic
431 adaptations to endurance training by several mechanisms that differ from the antioxidant
432 effects of vitamins C and E. Rather than acting as scavengers, they can stimulate stress-
433 related cell signaling pathways and increase the expression of genes encoding proteins, such
434 as NRF2, as well as by stimulating the SIRT1-AMPK-PGC1 α pathway in skeletal muscle,
435 leading to increased mitochondrial biogenesis (Fig. 2) [142]. Perhaps, paradoxically for the

436 endurance athlete, it is thought that AMPK activation relies on the ability of polyphenols,
437 such as quercetin and resveratrol, to directly bind and inhibit the mitochondrial F1F0-
438 ATPase/ATP synthase (Complex V), thus impairing ATP production [143]. A number of
439 studies have investigated the effect of polyphenols on exercise performance [142]; however,
440 there are few that have also included supervised endurance training programs (Table 4).

441

442 4.2.1 Resveratrol

443 Resveratrol is a polyphenol found in grapes, red wine, and other plant species and is known
444 to activate SIRT1 [110], and can shift muscle fibres towards a more oxidative phenotype
445 [144]. Resveratrol supplementation during eight weeks of HIIT in sedentary men blunted
446 the training-induced improvements in VO_{2max} and protein carbonylation, while having no
447 effect on *PGC-1 α* mRNA, CYT-C, CS and β -HAD activity, or time to exhaustion during a one-
448 legged knee-extensor test, compared with a placebo [145, 146]. In contrast, four weeks of
449 resveratrol supplementation by recreationally-active men performing HIIT resulted in no
450 differences in training-induced increases in VO_{2max} , peak aerobic power, Wingate power,
451 succinate dehydrogenase activity, or fibre-type distribution, compared to placebo, although
452 the resveratrol group had smaller increases in the gene expression of *PGC-1 α* , *SIRT1*, and
453 *SOD* [147]. This is in line with *in-vitro* research showing acute exposure to resveratrol
454 inhibits AMPK activity in human skeletal muscle cells [148]. Following 12 weeks of treadmill
455 training with resveratrol, rats bred for increased endurance capacity had increased
456 activation of the AMPK-SIRT1-*PGC-1 α* pathway and VO_{2max} [149], while rats bred for low
457 aerobic capacity had no differences in VO_{2max} , AMPK, or SIRT1 levels [150], suggesting the
458 response to resveratrol may be influenced by training status. The available data on

459 resveratrol are limited but suggest that active/trained humans and animals may respond
460 differently than those who are sedentary/untrained.

461

462 4.2.2 Green Tea Extract

463 Green tea extracts are a type of polyphenolic flavonoids which, beyond their role as an
464 antioxidant, may also play a role in the mobilisation and oxidation of fatty acids [151] that
465 appears to be mediated, at least in part, by reducing the malonyl-CoA content in skeletal
466 muscle [152]. Supplementing green tea extract during ten weeks of moderate-intensity
467 endurance training in healthy males resulted in greater fat oxidation while cycling at 55%
468 VO_{2peak} , with no changes observed in the placebo group [109] (Table 4). Untrained men who
469 performed a 4-week training intervention with green tea extract or placebo had similar
470 improvements in VO_{2max} and run to exhaustion time (8.1–9.7 km/h at 18-20% grade), with
471 no differences between groups for total antioxidant status [153]. However, these are
472 performance tasks that would not be expected to benefit from increased fat oxidation rates
473 as they are at an intensity that would be reliant on carbohydrate oxidation [154]. Mice that
474 underwent endurance training for 10 weeks with green tea extract supplementation had
475 better running (~2.5 h) and swimming (~40 min) times to exhaustion compared with the
476 exercise-only group, along with higher levels of muscle β -oxidation and *FAT/CD36* mRNA
477 [152, 155]. The limited data examining green tea extract in the context of endurance training
478 support the notion of increased fat oxidation and improvement in exercise time to
479 exhaustion in animals but not untrained men; however, studies that include other measures
480 of performance (e.g. time-trials) are needed, particularly at intensities and durations that
481 may favour improved fat oxidation.

482

483 *4.3 Other Antioxidants*

484 Supplementation with (-)-epicatechin, a component of cocoa known to activate the SIRT1
485 pathway [156], impaired training adaptations during four weeks of cycling training;
486 increases in $VO_{2\text{peak}}$ (+22.6%) and succinate dehydrogenase activity (+59.1%) were seen in
487 the placebo but not the supplement group, although no differences in peak power or CS
488 activity were observed between groups [157] (Table 4). In contrast, mice undergoing
489 treadmill training had greater increases in time to exhaustion, CS levels, and protein levels
490 of PGC-1 β and TFAM with (-)-epicatechin supplementation compared with exercise-only
491 [158]. The use of allopurinol (an inhibitor of xanthine oxidase) in rats for six weeks had no
492 effect on training-induced increases in PGC-1 α , TFAM, or CYT-C protein expression, or CS
493 and β -HAD enzyme activity, despite an attenuation of key signaling proteins (p38 MAPK,
494 ERK1/2, and TFAM) after a single session of exercise [103, 159], highlighting the importance
495 of studying longer-term adaptations to endurance training.

496

497 *4.4 Summary*

498 Endurance-related performance improvements following one- to six-month training
499 programs are not impacted by supplementation with vitamin C and/or vitamin E and are
500 unlikely to be affected by other antioxidants, although fewer data are available. Less clear
501 are the effects of vitamins C and E on markers of training adaptations and oxidative stress.
502 The disconnect between an impaired adaptive response without measurable performance
503 decrements may imply that longer time frames are needed before observable differences in
504 performance can be detected. Differences in training protocols, training status, and type and

505 amount of supplementation, may also be responsible for contrasting results, as well as
506 inherent redundancy in the mechanisms governing skeletal muscle adaptations to exercise.
507 ROS production is only one of the mechanisms by which adaptation is regulated, along with
508 contraction-induced changes in mechanical strain, ATP turnover, calcium flux, redox
509 balance, and intracellular oxygen pressure (Fig. 2) [3]. Although many studies report
510 attenuated levels of signaling molecules involved in mitochondrial biogenesis, increased
511 levels of CS activity suggest that changes in mitochondrial volume are not inhibited by
512 antioxidant supplementation [123, 159]. Future research should attempt to differentiate
513 between the antioxidant actions of a given supplement and other signaling pathways (e.g.
514 AMPK, SIRT1) that may be influenced.

515

516 **5. Caffeine**

517 Caffeine is well-studied and commonly reported to exhibit performance-enhancing effects
518 during endurance exercise [160]. When taken in moderate doses (3 to 6 mg/kg), 2 to 3%
519 improvements are seen in time-trial performance lasting 6 min to 2.5 h [160] and power
520 during HIIT [161]. It has been suggested that habitual caffeine usage will decrease its efficacy
521 [162]. However, caffeine supplementation (4 to 6 mg/kg) has improved 30- to 45-min
522 cycling time-trial performance in habitual low, moderate, and high caffeine consumers [163,
523 164], and the ingestion of 3 mg/kg for 20 days continued to produce an ergogenic effect
524 [165], suggesting that regular caffeine consumption during training sessions should not
525 reduce its longer-term impact. Despite its widespread use, little is known about the effects
526 of caffeine ingestion prior to exercise on subsequent adaptations to training.

527

528 There are several mechanisms that could lead to enhanced endurance training adaptations.
529 By way of reduced perception of exertion, likely through its effects as an adenosine receptor
530 antagonist [166], an athlete may be able to accumulate a greater training stress. Indeed,
531 participants who consumed 3 to 6 mg/kg caffeine completed 12.6% more work during 30
532 minutes of cycling at a given level of perceived exertion [167], increased power by 2.8%
533 during HIIT (8x5 min at maximum intensity with 1 min recovery) [161], and were able to
534 mitigate reductions in power during training sessions performed with low carbohydrate
535 availability [161]. Caffeine can increase exogenous carbohydrate oxidation [168], possibly
536 via greater intestinal absorption [169], and also increase AMPK activation via calcium-
537 mediated protein phosphatase 2A activity [170]. Emerging research also points to a role for
538 caffeine in improving mitochondrial respiration via its effects on mitochondrial p27 [171],
539 suggesting the potential to work synergistically with SIT - the form of interval training that
540 has been associated with the greatest improvements in mitochondrial respiration [172].
541 Taken together, caffeine has the potential to impact training adaptations across a number of
542 key pathways that can ultimately lead to greater increases in mitochondrial biogenesis (Fig.
543 2).

544

545 Despite the above rationale, only one study in humans, and one study in rats, has investigated
546 the effects of caffeine on adaptations to endurance training. In the human study, the caffeine
547 was part of a multi-ingredient supplement, dietary caffeine intake was not controlled for,
548 and there were no differences in caffeine consumption between groups [173], while rats
549 given caffeine prior to each exercise session during six weeks of HIIT were only studied for
550 changes in brain and behavioral biomarkers [174]. Research should investigate the effects

551 of caffeine on training adaptations, in conjunction with the impact of exercise intensity,
552 training status [175], sex [176], and genotype [177], using moderate (3 to 6 mg/kg) and low
553 (<3 mg/kg) [178] doses.

554

555 **6. Creatine**

556 Though creatine supplementation is rarely associated with endurance sports, it has been
557 shown to enhance exercise performance across a variety of sporting events (e.g. sprinting,
558 middle-distance, team sports, and HIIT in endurance sports [179]) and this has been
559 attributed to elevated muscle content of creatine and phosphocreatine [179]. A dose of 5 g
560 four times per day for 5 to 7 days is commonly used as a loading protocol, with subsequent
561 daily doses of 3 to 5 g/day to maintain elevated creatine levels [179]. However, high and low
562 responders to creatine supplementation have been identified, possibly due to variations in
563 baseline muscle creatine content [180], and/or its uptake and use [181]. Despite the
564 accepted role of creatine for improving performance, there has been little investigation of its
565 ability to affect adaptations to training.

566

567 There are several potential mechanisms by which creatine supplementation may be able to
568 affect training adaptations. Exercise intensity appears to be a key factor for training-induced
569 increases in mitochondrial respiration [172], and so any supplement that can increase
570 exercise intensity could potentially offer additional benefit to endurance training,
571 adaptation, and performance. In addition to its primary role of combining with a phosphoryl
572 group to form phosphorylcreatine via the creatine kinase reaction, creatine may also play a
573 role in aerobic energy metabolism by connecting sites of ATP production (glycolysis and

574 oxidative phosphorylation) with subcellular sites of ATP utilisation (ATPases) [182], with
575 subsequent enhancement of mitochondrial respiration in slow-twitch but not fast-twitch
576 fibres [183]. This may allow a greater amount of work to be completed during a training
577 session, and a reduced oxygen cost during submaximal exercise. Creatine has also been
578 shown to have antioxidant actions reducing the formation of ROS, oxidative DNA damage,
579 and lipid peroxidation after exercise, which may affect exercise-induced cell signaling [184].
580 There is a potential for increases in body mass due to water retention with creatine loading
581 [179]. However, despite a ~2.5% increase in body mass, well-trained cyclists undergoing
582 both creatine and carbohydrate loading reported a greater power output during sprint
583 efforts within a simulated 120-km time trial, with no differences in simulated uphill cycling,
584 compared to placebo [185].

585

586 Two studies using recreationally-active men performing four weeks of HIIT while
587 supplementing with either creatine (10 g/day) or a placebo reported significant
588 improvements in the creatine but not placebo groups for critical power and ventilatory
589 threshold (Table 5) [186, 187]. However, no differences were seen between groups for
590 VO_{2peak} , time to exhaustion at VO_{2peak} , anaerobic working capacity, or total work done during
591 a ride to exhaustion at 110% of peak aerobic power [186, 187]. Similar research in
592 recreationally-active women found no differences in exercise-induced improvements in
593 VO_{2peak} , ventilatory threshold, or 2-km time-trial performance (~2 min) [188]. However, that
594 study did not match menstrual phase, which has been shown to impact the blood lactate
595 response to high-intensity exercise [189]. Similar to other supplements, it is difficult to
596 separate the effects of creatine on performance from its effects on adaptations to training.

597 For example, in the absence of training, 5 to 7 d of creatine loading resulted in increases in
598 power at the lactate threshold [190] and supra-maximal time to exhaustion [190, 191], as
599 well as lower $\dot{V}O_2$ during sub-maximal cycling [191]. Thus, while creatine may improve some
600 adaptations to endurance training, the limited evidence does not yet support its widespread
601 use by endurance athletes. More research is needed, particularly in trained participants
602 performing 15-s to 4-min intervals using maximal efforts rather than pre-determined work
603 rates, while also controlling for the effects of the supplement alone (Table 2).

604

605 **7. Conclusion**

606 The most important variables impacting adaptations to endurance training are the training
607 stimuli - volume and intensity. However, within a given training paradigm, the appropriate
608 use of dietary supplements may offer additional benefits. These benefits appear largely by
609 allowing increasing training intensities, and so HIIT prescriptions should avoid pre-
610 determined workloads in favor of time-based intervals (e.g. 4-min maximal efforts). Beetroot
611 juice appears to impact skeletal muscle fibre-type remodeling, though more research with
612 concurrent endurance training is needed. Supraphysiological doses of antioxidants should
613 be used with caution as research is unclear regarding the extent of their effects on training
614 adaptations, but they appear unlikely to negatively affect performance in the short-term (<
615 6 months). Caffeine and creatine have potential for augmenting adaptations to endurance
616 training, although clear data are lacking.

617

618 Finally, it is imperative for athletes who compete under anti-doping rules to avoid
619 supplements that contain prohibited substances [192]. It is tempting to interpret small or

620 trivial effects in sport science research as unlikely to harm, but the risk of positive doping
621 tests should be weighed against the unproven effects of a supplement. Clearly, strong caution
622 must be used when athletes, coaches, and health care practitioners are selecting dietary
623 supplements for use.

Table 1: Overview of studies using buffering agents during supervised endurance training

	Participants	Training Status	Length	Supplement Dosage	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)	Adaptations (compared with placebo)
Sodium Bicarbonate								
Edge et al. 2006[33]	16 f	Recreationally Active	8 weeks	0.4 mg/kg body mass	HIIT 3x/wk; 6-12x 2-min cycle intervals at 140 – 170% of LT, 1 min RBI	24	Lactate threshold (LT): +26 vs. 15% ($d=0.5$, [95% CI -0.5, 1.5]) Time to fatigue: +164 vs. 123% ($d= 1.9$, [95% CI 0.7, 3.1]) No difference in or $VO_{2\text{ peak}}$	No differences in muscle buffer capacity
Driller et al. 2013[36]	12 m	Well-Trained	4 weeks	0.3 g/kg body mass	HIIT 2x/wk; 8 × 2.5-min rowing intervals at 90% of PPO, 3 min RBI	8	No differences in performance or LT	
Hawke et al. 2014[35]	19 m	Recreationally Active	6 weeks	0.4 g/kg body mass	HIIT 3x/wk; 8-12x 2-min cycling intervals at 85-110% $VO_{2\text{ peak}}$, 1 min RBI	18	No differences in performance or LT	CS activity +22.3 vs. 12.6%
Wang et al. 2019[34]	20 m	Recreationally Active	6 weeks	0.2 g/kg body mass	HIIT 3x/wk; 4 sets of 20-30 s cycling at 100% PPO, 30-40 s at 70% PPO, 1 min RBS	18	Greater improvement in Wingate relative peak power (20.8 vs. 10.3% ($d = 2.1$, [95% CI 1.0, 3.2])) No differences in Wingate relative mean power	Increased peak lactate concentration only in the sodium bicarbonate group
Bishop et al. 2010[37]	21 m rats	N/A	5 weeks	0.05 g/kg body mass	HIIT 5x/wk; 7-12 × 2 min treadmill intervals, 1 min RBI	25	Time to fatigue: 12-fold vs. 8-fold longer than control ($d= 11.1$, [95% CI 6.8, 15.3])	Greater improvements in mitochondrial mass and respiration ($d= 1.8$, [95% CI 0.6, 3.1])
Beta-alanine								
Smith et al. 2009[57]	46 m	Recreationally Active	6 weeks	3 weeks at 6 g/day followed by 3 weeks at 3 g/day	HIIT 3x/wk; 5-6x 2-min cycle intervals at 90-115% PPO, 1 min RBI	18	No difference in $VO_{2\text{ peak}}$ Time to exhaustion at 110% PPO: +18.7 vs. 15.1% ($d= 0.3$, [95% CI -0.4, 0.9])	
Walter et al. 2010[54]	44 f	Recreationally Active	6 weeks	3 weeks at 6 g/day followed by 3 weeks at 3 g/day	HIIT 3x/wk; 5x 2-min cycle intervals at 90-110% PPO, 1 min RBI	18	No difference in $VO_{2\text{ max}}$ or power at ventilatory threshold	
Bellinger et al. 2012[61]	14 m	Well-Trained	4 weeks	65 mg/kg body mass/day	HIIT 2x/wk; 8 × 2.5 min cycling intervals at 90% $VO_{2\text{ max}}$ HR	8	No differences in 4-min time-trial power	

Howe et al. 2013[59]	16 m	Well-Trained	4 weeks	4.5 g/day	HIIT 2x/wk; 8x 2.5 min at 90%PPO, 3 min RBI	8	No differences in 4-min time-trial power, trend for increased total work done (p=0.09)	
Cochran et al. 2015[55]	24 m	Recreationally Active	6 weeks	4 weeks loading with 3.2 g/day, followed by 6 weeks of 3.2 g/day with supervised training	SIT 3x/wk; 4–6 Wingate tests, 4 min RBI	18	No difference in VO _{2peak} , repeated-sprint capacity, or time trial performance	No difference in cytochrome-c oxidase or β-HAD maximal activities
Bellinger and Minahan 2016[53]	14 m	Well-Trained	5 weeks	4 weeks loading with 6.4 g/day, followed by 5 weeks of 1.2 g/day with supervised training	SIT 2x/wk; 4-6x 1-km (~1.3 min) cycling sprints, 4 min RBI	10	No difference in TT performance or VO _{2max} Training intensity: +9.9 vs. 4.9% (d= 0.3, [95% CI -0.8, 1.3]) Time to exhaustion at 120% PPO: +14.9 vs. 9.0% (d= 0.5, [95% CI -0.6, 1.58])	
Santana et al. 2018[58]	16 m	Recreationally Active	23 days	5 g/day	Moderate intensity 2x/wk (7-12 km), HIIT 1x/wk (6x500 m sprints, 2 min RBI)	9	10 km running performance: -6.7% vs. no change	
Wang et al. 2018[56]	38 m	Recreationally Active	4 weeks	6.4 g/day	HIIT 2x/wk; three sets of 5x10 s maximal sprints, 20 s RBI, 5 min RBS	8	No difference in VO _{2max} or PPO Anaerobic capacity: 14% higher than placebo (d = 0.8, [95% CI -0.1, 1.8])	
HIIT: High-intensity interval training, SIT: sprint-interval training, TTE: Time to exhaustion, PPO: Peak power output, RBI: Rest between intervals, RBS: Rest between sets Effect size of supplement calculated as Cohen's d when data were available (reported as effect size, 95% CI)								

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625

Table 2. Proposed mechanisms and recommendations for studying endurance training adaptations

	Mechanisms of action	Ingestion	Type of training	Outcome measures
Sodium bicarbonate	<ul style="list-style-type: none"> - Increased training intensity - Increased pH --> improved mitochondrial adaptations 	0.2-0.4 g/kg body weight - sufficient to raise blood [HCO ₃ ⁻] by 5-6 mmol	Interval training sufficient to elevate lactate levels and/or pH compared with a placebo	<ul style="list-style-type: none"> - Lactate threshold - Mitochondrial mass and respiration - Time to fatigue at maximal or near-maximal efforts - Time-trial performance
Beta-alanine	<ul style="list-style-type: none"> - Increased training intensity - Increased pH --> improved mitochondrial adaptations - Improved Ca sensitivity - Reduced lipid peroxidation 	2-4 wk loading phase of 4-6 g/d, followed by 3-6 g/d	1 to 4 min intervals using maximal efforts rather than pre-determined work rates, sufficient to elevate blood lactate compared with a placebo	<ul style="list-style-type: none"> - Open-ended exercise tests (e.g. time to exhaustion) rather than fixed end-point tasks (e.g. time trials) - Training intensity - Oxidative stress
Dietary nitrate	<ul style="list-style-type: none"> - Increased training intensity - Increased mitochondrial biogenesis via nitric oxide signaling and possibly RONS - Reduced oxygen cost - Muscle fibre-type remodeling 	8-13 mmol/d from beetroot juice	15 s to 4 min intervals using maximal efforts rather than pre-determined work rates, steady-state endurance	<ul style="list-style-type: none"> - Mitochondrial mass and respiration - Muscle fibre-type changes - Training intensity - VO_{2max}
Antioxidants	<ul style="list-style-type: none"> - Reduced oxidative stress leading to improved training and recovery - Stimulate or impair stress-related signaling pathways Stimulate mitochondrial biogenesis 	More research needed before recommendations can be made, particularly with regard to timing relative to exercise	More research needed before recommendations can be made	<ul style="list-style-type: none"> - Mitochondrial adaptations - Performance changes - Training intensity
Caffeine	<ul style="list-style-type: none"> - Increased training intensity via decreased perception of exertion - Improved Ca sensitivity - Increased AMPK signaling 	2-6 mg/kg	0.5 to 4 min intervals using maximal efforts rather than pre-determined work rates	<ul style="list-style-type: none"> - Mitochondrial mass and respiration - Training intensity
Creatine	<ul style="list-style-type: none"> - Increased training intensity - Improved energy production - Reduced lipid peroxidation 	10 g/d for 10 d, then 10 g/d on training days only - more research needed	15 s to 4 min intervals using maximal efforts rather than pre-determined work rates	<ul style="list-style-type: none"> - Mitochondrial respiration - Training intensity - Time-trial performance

Table 3: Overview of studies using dietary nitrate during supervised endurance training

	Participants	Training Status	Length	Supplement Dosage	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)	Adaptations (compared with placebo)
Puype et al. 2014[83]	22 m	Moderately Trained	6 weeks	~5 mmol per day (0.07 mmol NO ₃ ⁻ /kg body mass)	30 min at 4-6 mmol/L blood lactate, 5x/wk in normobaric hypoxia	30	No difference in VO _{2max} , LT, or time-trial performance	
De Smet et al. 2016[77]	27 m	Recreationally Active	5 weeks	6.5 mmol NaNO ₃	SIT 3x/wk in normobaric hypoxia; 4-6 Wingate tests, 4.5 min RBI	15	No difference in VO _{2max} , LT, or time-trial performance	Increased percentage of type IIa fibres No difference in CS activity
Muggeridge et al. 2017[84]	27 m	Recreationally Active	3 weeks	~8 mmol nitrate [0.06–0.15 mmol/kg body mass]	SIT 3x/wk; 4-6x 15 s maximal sprints, 4 min RBI	9	Maximal work rate during incremental exercise: +8.7 vs. 4.7% (<i>d</i> = 0.3, [95% CI -0.6, 1.2]) No difference in VO _{2max}	
Thompson et al. 2017[75]	18 m, 18 f	Recreationally Active	4 weeks	12.8 mmol NO ₃ ⁻ per day (2 servings of 6.4 mmol, AM/PM)	SIT 3-4x/wk; 4-5 Wingate tests, 4 min RBI	14	VO _{2peak} : +8.8 vs 2.0% (<i>d</i> = 0.2, [95% CI -0.6, 1.0]) Maximal work rate during incremental exercise: +7.7 vs. 5.0% (<i>d</i> = 0.1, [95% CI -0.7, 0.9]) No difference in time to fatigue at high intensity	Decreased proportion of type IIx muscle fibres in the vastus lateralis
Thompson et al. 2018[85]	18 m, 12 f	Recreationally Active	4 weeks	12.8 mmol NO ₃ ⁻ per day (2 servings of 6.4 mmol, AM/PM)	SIT 3-4x/wk; 4-5 Wingate tests, 4 min RBI	14	VO _{2 peak} : +10.7 vs. 5.6% (<i>d</i> = 0.2, [95% CI -0.7, 1.0]) Time to fatigue: +71 vs. 47% (<i>d</i> = 0.4, [95% CI -0.5, 1.3]) No difference in maximal work rate during incremental exercise	
Finkel et al. 2018[87]	17 m	Recreationally Active	3 weeks	~11 mmol per day (0.14 mmol NaNO ₃ ⁻ /kg body mass)	HIIT 3x/wk; 45 intervals of 30 s at 10 w below W _{max} , 30 s recovery at 10 w	9	No differences in VO _{2max} , W _{max} , or time to exhaustion at 80% W _{max} Only placebo increased power during first of a dual Wingate test (6%; <i>d</i> = -0.5, [95% CI -1.4, 0.5]), similar improvements for second test	
Santana et al. 2019[86]	16 m	Recreationally Active	4 weeks	~12 mmol per day (across three servings)	Moderate intensity 2x/wk (5-12 km), HIIT 1x/wk (4-6x500 m sprints, 2 min RBI), weekly 10-km time-trial	12	"10-km running time: -9.1 vs. -1.0% (<i>d</i> = 1.2, [95% CI -2.3, -0.2]) No differences in 60-s Wingate test"	Lower lactate during 10-km time-trial

HIIT: High-intensity interval training, SIT: sprint-interval training, TTE: Time to exhaustion, PPO: Peak power output, RBI: Rest between intervals, W_{max}: Maximal aerobic wattage
Effect size of supplement calculated as Cohen's *d* when data were available (reported as effect size, 95% CI)

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Table 4: Overview of studies using antioxidant supplements during supervised endurance training

Humans	Supplement	Supplement Dosage	Participants	Training Status	Length	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)	Metabolic Adaptations (compared with placebo)	Oxidative Stress (compared with placebo)
Sharman et al. 1971[114]	Vitamin E	400 mg	26 m	Trained	6 weeks	4x/wk Competitive swim training - unspecified	24	No difference in 1 mi run or 400 m swim times		
Lawrence et al. 1975[115]	Vitamin E	900 iu	48	Well-trained	6 months	Competitive swim training - unspecified	Unspecified	No difference in 500 yd or 100 yd swim times		
Rokitzki et al. 1994[116]	Vitamin E	330 mg	30 m	Well-trained	5 months	Competitive cycling training - unspecified	Unspecified	No difference in LT		Reduced MDA
Oostenbug et al. 1997[117]	Vitamin E and fish oil	300 iu	24 m	Well-trained	3 weeks	Competitive cycling training - unspecified	Unspecified	No difference in VO_{2max} maximal workload, or 1-hr time-trial		
Gomez-Cabrera et al. 2008[118]	Vitamin C	1000 mg	14 m	Sedentary	8 weeks	3x/wk; 40 min steady-state cycling at 65-80% VO_{2max}	24	Trend for smaller improvement in VO_{2max} : +10.7 vs. 22% ($d = -1.1$, [95% CI -2.2, 0.04])		
Roberts et al. 2011[120]	Vitamin C	1000 mg	15 m	Recreationally Active	4 weeks	4x/wk HIIT; 5x3 min treadmill running at 90% VO_{2max} , 3 min RBI	16	No difference in VO_{2max} or 10-km time-trial performance	No difference in substrate utilization	
Braakhuis et al. 2014[119]	Vitamin C	1000 mg	23 f	Trained	3 weeks	3x/wk running; 4x 3-5 min and 6x2 min hill repeats	10	No difference in 5-km time trial		Increased protein carbonyl at rest, increased SOD post-exercise, blunting training-induced decrease in resting CAT activity
Bryant et al. 2003[121]	Vitamin C and E	1000 mg vit C, 400 iu/kg vit E, or 1000 mg vit C + 200 iu/kg vit E	7 m	Trained	3 weeks	Competitive cycling training, 250–350 km/wk	Unspecified	No difference in work completed	No difference in substrate oxidation	Vit C Increased MDA, no difference with vit C+E
Ristow et al. 2009[127]	Vitamin C and E	1000 mg vit C, 400 iu vit E	39 m	Trained and Untrained	4 weeks	5x/wk; 20 min biking or running, 45 min circuit training	20		Decreased PGC-1 α , PGC-1 β , PPAR γ , SOD, and GPx	

Yfanti et al. 2010,[123] 2011[124]	Vitamin C and E	500 mg vit C, 400 iu vit E	21 m	Recreationally Active	12 weeks	5x/wk cycling; one day each of graded exercise test; 10x3 min at 85% PPO, 3 min RBI; 1x60 min at 60% PPO; 5x8 min at 75% PPO, 4 min RBI; 1x120 min at 55% PPO	60	No difference in VO _{2max} , maximal workload, or LT	No difference in CS, β-HAD, PGC-1α, or PPARγ	No difference in SOD
Paulsen et al. 2014 [122] Cumming et al. 2014[126]	Vitamin C and E	1000 mg vit C, 235 mg vit E	26 m, 28 f	Trained	11 weeks	3-4 w/wk running; 2 days steady state 30-60 mins at 72-87% HR max, 2 days 4-6 x 4-6 min >90% HR max	41	No difference in VO _{2max} or shuttle run test	Decreased PGC-1α and COX-IV	Decreased uric acid No difference in GPx, SOD, GSH, or HSP70
Morrison et al. 2015[125]	Vitamin C and E	1000 mg vit C, 400 iu vit E	11 m	Recreationally Active	4 weeks	3x/wk cycling, 10x4 min at 90% VO _{2max} , 2 min RBI	12	No difference in VO _{2max}	No difference in CS or COX-IV Decreased TFAM	Decreased SOD
Shill et al. 2016[193]	Coenzyme Q10	10 mg MitoQ (proprietary CoQ-10)	20 m	Recreationally Active	3 weeks	3-5x/wk cycling, 45-60 min at 50-70% VO _{2max}	13	No difference in VO _{2max}	No difference in mitochondrial function	No difference in MDA
Ichinose et al. 2011[109]	Green tea extract	578 mg tea catechins	20 m	Recreationally Active	10 weeks	3x/wk cycling, 60 min at 60% VO _{2max}	30		Increased fat utilization	
Kuo et al. 2015[153]	Green tea extract	207 mg tea catechins	40 m	Sedentary	4 weeks	3x/wk running, 20 min at 75% oxygen uptake reserve	12	No difference in VO _{2max} or time to exhaustion		No difference for MDA or total antioxidant status
Scribbans et al. 2014[147]	Resveratrol	150 mg	16 m	Recreationally Active	4 weeks	3x/wk HIIT cycling, 8x20 s at 170% PPO, 10 s RBI	12	No difference in VO _{2max} , peak aerobic power, or Wingate power	No difference in succinate dehydrogenase activity Decreased gene expression of PGC-1α, SIRT1, and SOD	
Gliemann et al. 2013 [145] Oleson et al. 2014 [146]	Resveratrol	250 mg	27 m	Sedentary	8 weeks	2x/wk HIIT cycling, 1x/wk Crossfit (unspecified)	24	Smaller increase in VO _{2max} : +12.8 vs. 17.2% (<i>d</i> = -1.4, [95% CI -2.2, -0.5]) No difference in time to exhaustion	No difference in on PGC-1α mRNA, CYT-C, CS and β-HAD activity	Increased protein carbonyls
Polley et al. 2016[194]	Resveratrol	500 mg Resveratrol + 10 mg piperine	9 m, 7 f	Recreationally Active	4 weeks	3x/wk, 30 min forearm wrist flexor exercises	12		Increased mitochondrial oxidative capacity	
Schwarz et al. 2018[157]	Epicatechin	200 mg	20 m, f	Recreationally Active	4 weeks	4x/wk cycling, 2x 45-60 min at 50% W _{max} , 1x/wk HIIT, 1x/wk SIT	16	Smaller increase in VO _{2max} : +6.1 vs. 22.6% (<i>d</i> = -0.6, [95% CI -1.5,	Only placebo increased succinate	

									0.4]), no difference in peak aerobic power	dehydrogenase activity (+59%)	
Animals											
Venditti et al. 2014[128]	Vitamin E	700 mg/kg	32 m	Rats	10 weeks	5x/wk; 15-60 min/d swimming	50			Decreased mitochondrial respiration, NRF-1, NRF-2, PGC-1	Increased protein carbonyls Decreased GPx, glutathione reductase
Asha Devi et al. 2003[134]	Vitamin E	50 iu/kg	46 m	Rats	12 weeks	5x/wk; 5-30 min/d swimming with a load of 3% body mass tied to tail	60	Time to exhaustion: +33%			
Kim et al. 2017[132]	Vitamin C	500 mg/kg	24 m	Rats	4 weeks	5x/wk; 2 sessions per d swimming for 3 h per session, 45 min rest between sessions	40	No difference in time to exhaustion		No difference in phosphorylation of p38 MAPK and AMPK, or levels of PGC-1a, NRF-1, TFAM	Decreased thiobarbituric acid-reactive substance (TBARS)
Gomez-Cabrera et al. 2008[118]	Vitamin C	500 mg/kg	24 m	Rats	6 weeks	5x/wk; 85 min/d treadmill running at 75% VO2max	30	Time to exhaustion: +27 vs. 187% ($d = -19.1$, [95% CI -26.8, -11.4]) Trend for smaller improvement in VO2max: +4.6 vs. 17.1% ($d = -0.9$, [95% CI -2.1, 0.3])		Reduced expression of NRF-1, TFAM, SOD and GPx	
Higashida et al. 2011[131]	Vitamin C and E	750 mg/kg vit C, 150 mg/g vit E	18 m	Rats	3 weeks	6x/wk; 2 sessions per d swimming for 3 h per session, 45 min rest between sessions	36			No difference in mitochondrial enzymes	Decreased TBARS No difference in SOD1 or SOD2
Meier et al. 2013[129]	Vitamin C, Coenzyme Q10, N-acetylcysteine	140 mg/l vit C, 12mg/l of co-Q10 and 1% NAC	32 m	Mice	4 weeks	5x/wk; 45 min treadmill running	20	No difference in peak power		No difference in CS Decreased expression of SOD1, PGC-1a, or CD36 Increased expression of FABP-3	

Abadi et al. 2013[133]	Vitamin E, Coenzyme Q10, alpha lipoic acid	Standard chow with vitamin E (α-tocopherol, 1000 IU), 0.1% α-lipoic acid, and 0.25% CoQ10	36 m, 36 f	Mice	7 weeks	3x/wk; 30-45 min treadmill running	21	No difference in time to exhaustion	No difference in mitochondrial respiratory capacity, CYT-C, PGC-1α	No difference in CAT, SOD1, or SOD2
Strobel et al. 2011[130]	Vitamin E, alpha lipoic acid	1000 iu vit E/kg, 1.6 g/kg ALA	48 m	Rats	14 weeks	4x/wk; 90 min treadmill running at 70% VO ₂ max	56		Decreased PGC-1α mRNA, PGC-1α and COX IV protein, and CS activity	No difference in GPx, xanthine oxidase, or MDA
Wadley et al. 2013[159]	Allopurinol	0.25 mg/ml	24 m	Rats	6 weeks	5x/wk; 20-90 min treadmill running	30		No difference in NRF-2, GLUT4, or SOD mRNA, or PGC-1α, TFAM, CYT-C, CS, and B-HAD	No difference in SOD2
Lee et al. 2015[158]	Epicatechin	1 mg/kg, twice daily	34 m	Mice	8 weeks	5x/wk; 60 min treadmill running at 60% intensity	40	Time to exhaustion: 84 vs. 45% (<i>d</i> = 18.0, [95% CI 11.8, 24.3])	Increased CS activity, increased PGC-1B, TFAM	
Dolinsky et al. 2012[195]	Resveratrol	4 g/kg	24 m	Rats	12 weeks	5x/wk; 60 min treadmill running	60	21% longer time to exhaustion (<i>d</i> = 1.5, [95% CI 0.5, 2.4])	Increased CS activity, phosphorylation of AMPK, and PGC-1α expression	
Hart et al. 2013[149]	Resveratrol	100 mg/kg	24 m	Rats (bred for high endurance capacity)	12 weeks	5x/wk; 60 min treadmill running	60	VO ₂ max: ~18% increase (<i>d</i> = 2.4, [95% CI 0.9, 3.9]), 29% greater running distance during VO ₂ max test	Increased AMPK and SIRT1, decreased PGC-1α	
Hart et al. 2014[150]	Resveratrol	100 mg/kg	24 m	Rats (bred for low endurance capacity)	12 weeks	5x/wk; 60 min treadmill running	60	No difference in VO ₂ max		
Kan et al. 2016[196]	Resveratrol	25 mg/kg	16 m	Mice	4 weeks	7x/wk; 30 min swimming	28	No difference in swim time to exhaustion		
Murase et al. 2005[155]	Green tea extract	0.2-0.5% (wt/wt)	80 m	Mice	10 weeks	2x/wk; 30 min swimming	20	24% longer time to exhaustion (<i>d</i> = 2.3, [95% CI 1.2, 3.5])	Increased B-oxidation	
Murase et al. 2006[152]	Green tea extract	0.2-0.5% (wt/wt)	32 m	Mice	8 weeks	3x/wk; 30 min treadmill running	24	30% longer time to exhaustion (<i>d</i> = 1.9, [95% CI 0.7, 3.0])	Increased B-oxidation	

HIIT: High-intensity interval training, HR: Heart rate, SIT: sprint-interval training, TTE: Time to exhaustion, PPO: Peak power output, LT: Lactate threshold, RBI: Rest between intervals

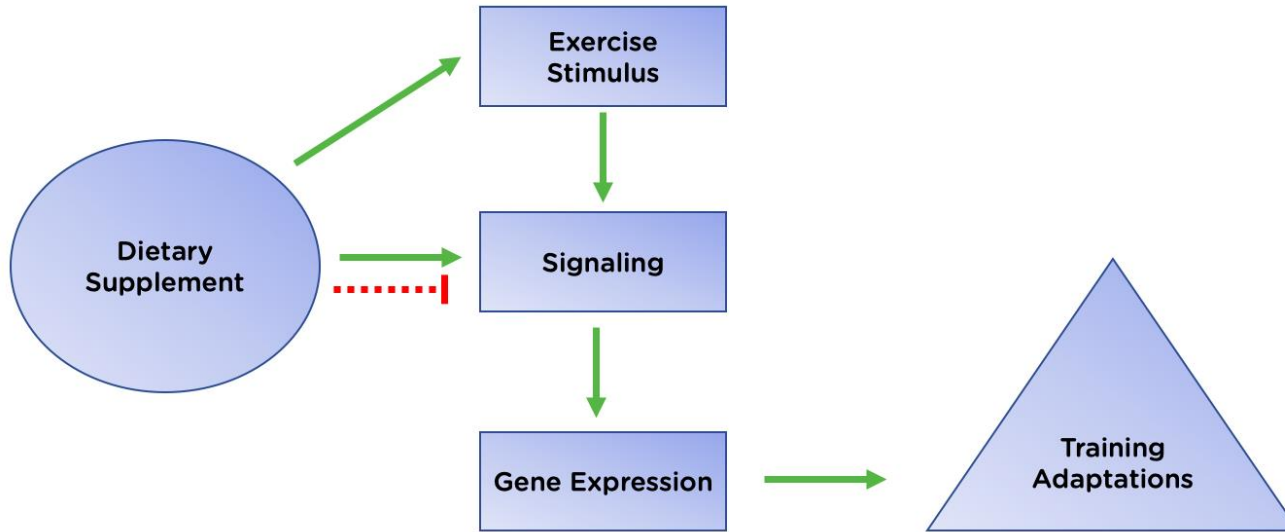
Effect size of supplement calculated as Cohen's d when data were available (reported as effect size, 95% CI)

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Table 5: Overview of studies using creatine supplementation during supervised endurance training

	Participants	Training Status	Length	Supplement Dosage	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)
Creatine							
Graef et al. 2009[187]	33 m	Recreationally Active	4 weeks	10 g per day for the first 10 days, then 10 g per day 5x/wk for three weeks (training days only)	Training 5/wk; 3/wk HIIT, 5x2 min at 90-120% PPO, 1 min RBI; 2x/wk recovery, 5x2 min at 80% PPO, 1 min RBI	20	Ventilatory threshold: +16% vs. 10% ($d=0.2$, [95% CI -0.5, 0.9]) No difference in VO_{2peak} , TTE at VO_{2peak}
Kendall et al. 2009[186]	42 m	Recreationally Active	4 weeks	10 g per day for the first 10 days, then 10 g per day 5x/wk for three weeks (training days only)	Training 5/wk; 3/wk HIIT, 5-6x2 min at 90-120% PPO, 1 min RBI; 2x/wk recovery, 5x2 min at 80% PPO, 1 min RBI	20	Critical power (w): +6.7% vs. no change in control ($d = 0.1$, [95% CI -0.6, 0.8]) No changes in anaerobic working capacity
Forbes et al. 2017[188]	17 f	Recreationally Active	4 weeks	0.3 g/kg body mass/ day for 5 days followed by 0.1 g/kg body mass for 23 days	HIIT 3x/wk; 1 session of 4-6 Wingate tests, 4 min RBI; 1 session of 10-20 6 s sprints, 24 s recovery; 1 session of 8-12x 60 sec at 85% and 60 sec at 15% PPO	12	No difference in VO_{2max} , LT, or time trial performance
HIIT: High-intensity interval training, TTE: Time to exhaustion, PPO: Peak power output, RBI: Rest between intervals Effect size of supplement calculated as Cohen's d when data were available (reported as effect size, 95% CI)							

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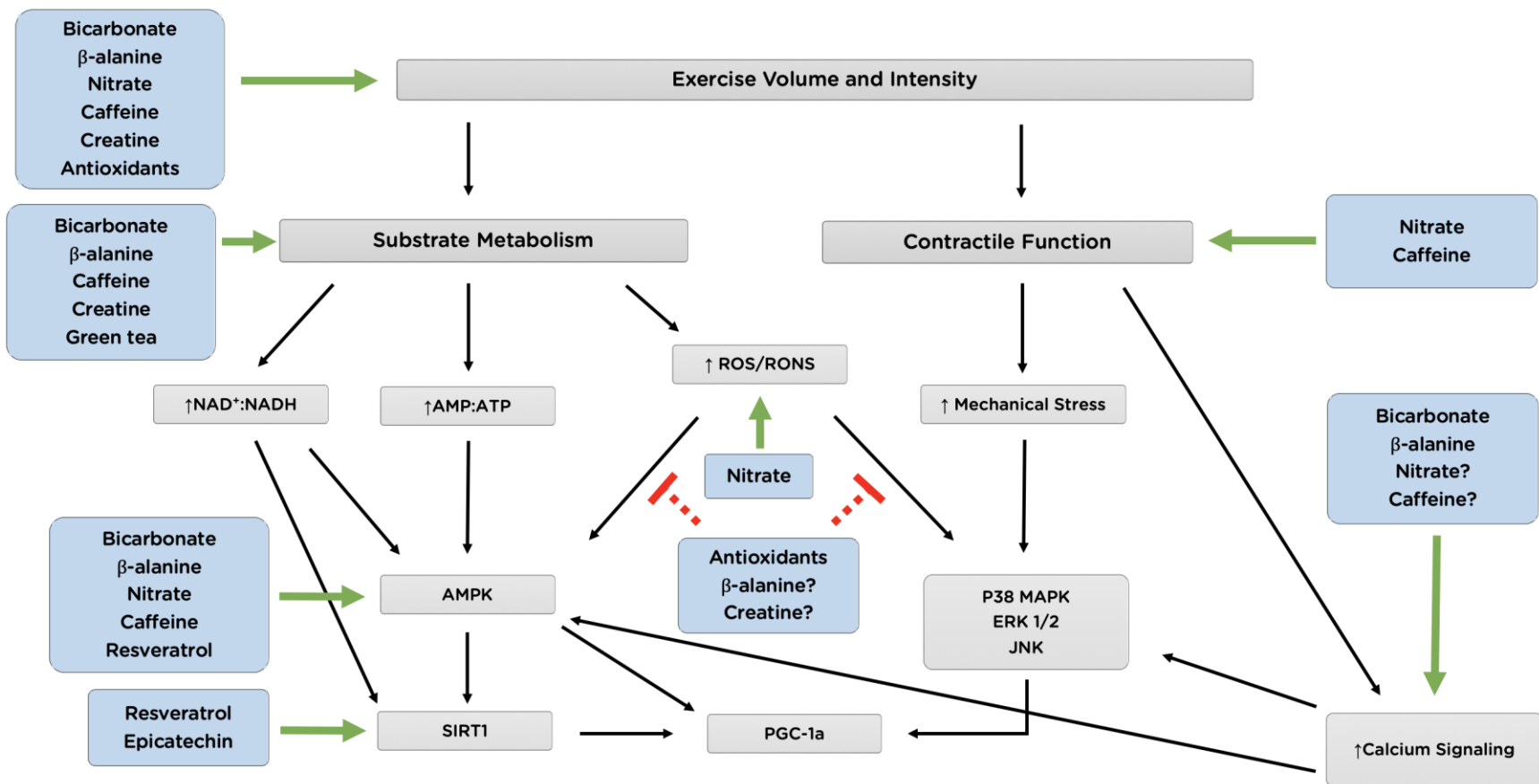


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635 Figure 1. Potential impact of supplements on endurance training adaptations

636 Green solid line: increases, Red dashed line: inhibits

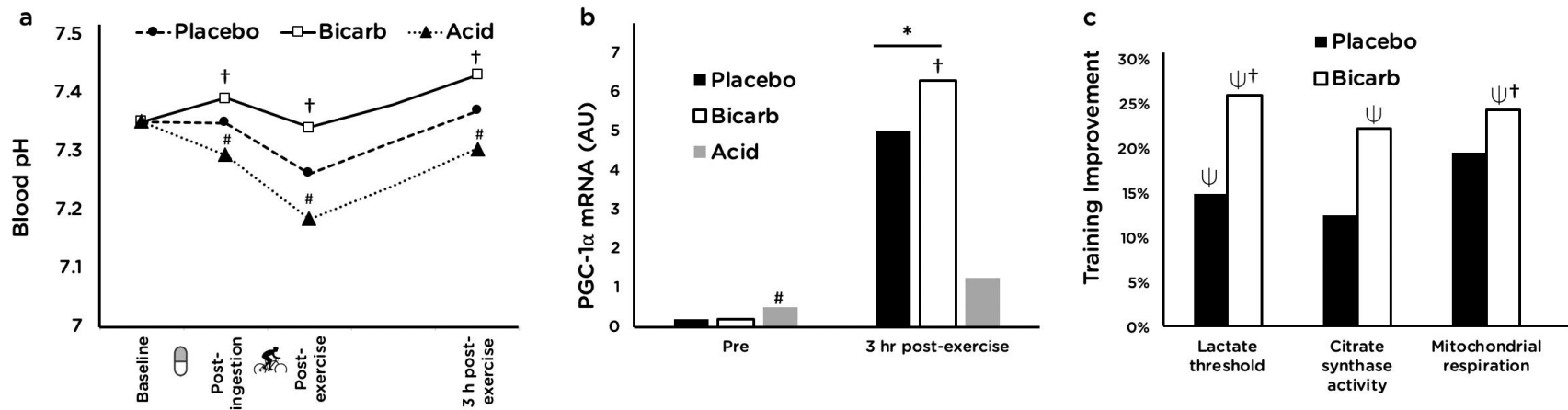
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Figure 2. Schematic of areas where dietary supplements have the potential to impact the adaptive responses to endurance training

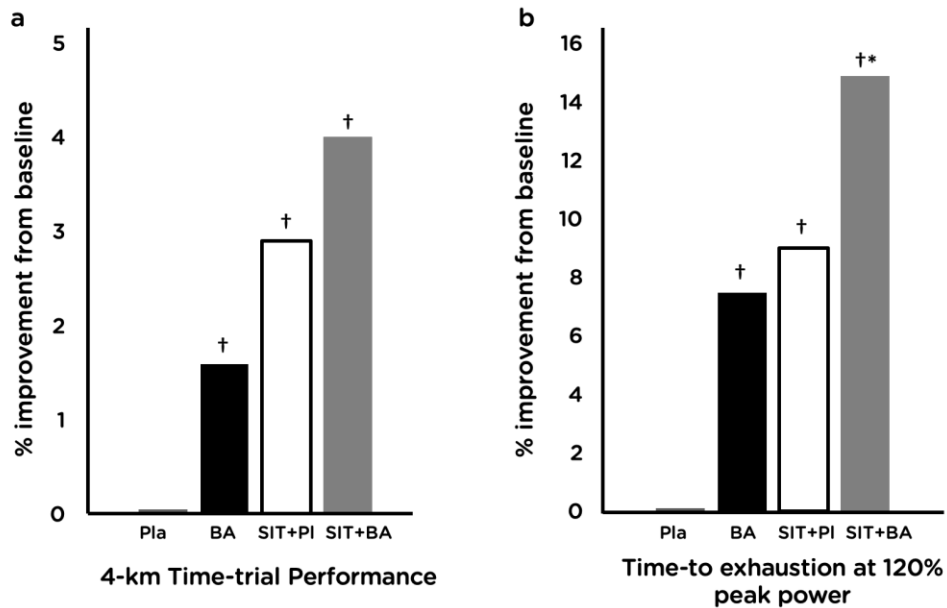
AMP adenosine monophosphate, AMPK 5' AMP-activated protein kinase, ERK1/2 extracellular-regulated kinase 1 and 2, NADH nicotinamide adenine dinucleotide, p38 MAPK p38 mitogen-activated protein kinase, PGC-1 α peroxisome proliferator-activated receptor γ coactivator 1 α , RONS reactive oxygen and nitrogen species, SIRT1 silent mating type information regulation 2 homolog 1. Green solid line: increases, Red dashed line: inhibits. ?= mechanistic potential to occur



647

648 Figure 3. **a** Blood pH responses to high-intensity interval training with ingestion of sodium bicarbonate (Bicarb), ammonium
 649 chloride (Acid), or a placebo, **b** effect of pH and training on PGC-1 α , and **c** training responses. An alkaline pH can enhance, while
 650 a more acidic pH can impair, the acute mRNA response of PGC-1 α and longer-term training adaptations to high-intensity interval
 651 training. PGC-1 α : peroxisome proliferator-activated receptor γ coactivator 1 α . *Main effect for time compared with pre-
 652 ingestion ($P < 0.01$); †Significant difference from placebo at the time point designated ($P < 0.01$); # Significantly different from
 653 placebo and bicarb at the time point designated ($p < 0.05$); Ψ significant difference from pre-training ($p < 0.05$). Adapted from
 654 [22, 27, 33, 35, 37].

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657 Figure 4. Percent improvement in **a** 4-km time-trial performance and **b** time to exhaustion after 4-wk of placebo and regular
 658 training (Pla), 4-wk of beta-alanine supplementation and regular training (BA), 5-wk of sprint-interval training and placebo
 659 (SIT+Pla), 4-wk loading phase of beta-alanine followed by 5-wk of sprint-interval training with continued supplementation
 660 (SIT+BA), in trained cyclists. Supplementing with β -alanine while maintaining their normal training (BA) reported a 1.6%
 661 improvement in 4-km time-trial performance (~ 6 min) ($d = 0.3$) and a 7.5% improvement in time-to-exhaustion at 120% of
 662 peak power ($d = 0.4$), compared with no changes in the placebo group, while five weeks of SIT with β -alanine resulted in a greater
 663 improvement in time-to-exhaustion (+14.9 vs. 9.0%, $d = 0.5$) and a trend for greater improvement in time-trial performance
 664 compared with a placebo, suggesting both independent and additive benefits of SIT and β -alanine supplementation. †Significant
 665 difference from pre-supplementation ($P < 0.05$), *Significant difference from SIT+Pla. Adapted from [53, 60].

666

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671

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