1   Title of Article: Effect of New Zealand Blackcurrant on Blood Pressure,

2   Cognitive Function and Functional Performance in

3   Older Adults.

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26   **ABSTRACT**

27   New Zealand blackcurrant (NZBC) can increase exercise performance in young adults,

28   potentially by anthocyanin-induced cardiovascular function alterations and increased

29   blood flow, however effects upon blood pressure, functional exercise performance and

30   cognitive function in older adults is unknown. In a randomised, double-blind, placebo-

31   controlled, cross-over design, 14 older adults (age: 69±4 years, height: 172±9 cm, body

32   mass: 85±12) ingested NZBC extract (600 mg·day^{-1} CurraNZ™) or placebo (PL, 600

33   mg microcrystalline cellulose) for 7-days (7-day washout between conditions). On day-

34   7, 2-hours following consumption of the capsules, resting blood pressure, cognitive

35   function (Cambridge neuropsychological test automated battery) and 6-minute walk

36   test performance and were measured. Intake of NZBC caused a decrease ($P<0.05$) in

37   systolic (PL: 136±14; NZBC: 130±12 mmHg) and diastolic (PL: 84±11; NZBC 78±6

38   mmHg) blood pressure. There was no effect on 6-minute walk performance or cognitive

39   function variables. Future research should address optimisation of intake and examine

40   cardiovascular responses during exercise.

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42   **Keywords**: New Zealand blackcurrant; anthocyanins; cognitive function; functional

43   performance; older adults.

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INTRODUCTION

Ageing is a universal process that is associated with a deleterious decline in physical and cognitive function.[1] Cognitive function decrements include processing speed, working memory capacity and inhibitory processes, however implicit memory and knowledge storage are less effected.[2] Physical impairments in older adults are partly resultant of sarcopenia and reduced cardiovascular capacity and these have implications for functional performance in activities of daily living.[3] As a result, interventions that can promote cognitive function and functional performance are of interest.

Anthocyanins act as natural pigments within fruits and vegetables, and observational studies have identified causal links between their intake and disease risk such as cardiovascular disease and type-2-diabetes.[4,5] Mechanisms for these observations are likely multifactorial, including anti-oxidative and anti-inflammatory effects, and their ability to alter signalling pathways.[6] There have been observations of anthocyanins having positive effects upon age-associated cognitive decline in adults over 65 years old.[7] Mechanisms for effects upon cognitive function by anthocyanins are unclear, however may result from effects upon an increase in blood flow to the brain. For example, Bowtell et al[8] observed 12 weeks of blueberry concentrate supplementation providing 387 mg·day^{-1} increased brain activity within Brodmann areas 4/6/10/21/40/44/45, precuneus, anterior cingulate and insula/thalmus in older adults. In addition, Bowtell et al[8] also observed increased perfusion of the parietal and occipital lobes with blueberry supplementation.

What is more, observations have shown anthocyanins and their metabolites to have an inhibitory effect upon monoamine oxidase (MAO).[9] These enzymes metabolise monoamines and as a result produce hydrogen peroxide. Inhibition may therefore reduce oxidative stress and in turn lead to an increase in monoamines which are needed

76   for healthy cognitive function. More recently, Watson et al[10] observed an almost

77   complete inhibition of MAO-B activity (96%), a reduction in plasma normeadrenaline

78   concentration (60%) and an increase in dihydroxyphenylglycol (~35.5%) 2.5 hours

79   following blackcurrant juice treatment in healthy young (18-35 years) adults. This was

80   also coupled with an attenuation of an increase in the cognitive function variable, digit

81   vigilance reaction times with blackcurrant supplementation and trends in Bond-Lader

82   alertness ratings and mental fatigue. Therefore, these effects may extend to older adults

83   and have similar positive effects upon cognitive function.

84   In healthy young adults (i.e. <45 years), blackcurrant anthocyanins have been shown to

85   increase peripheral blood flow and reduce muscle fatigue during typing activity and

86   increase femoral artery diameter during isometric exercise.[11,12] Therefore, if

87   anthocyanins can increase blood flow in older adults, improvements in functional tasks

88   that require provision of energy from aerobic pathways may be observed. For older

89   adults this is possible as blood flow is reduced to muscle in comparison to young adults

90   and aerobic capacity is decreased.[13,14] What is more, in younger adults New Zealand

91   blackcurrant extract has shown positive benefits to exercise performance in both

92   cycling and running.[15–19] Therefore, the primary aim of the present study was to

93   examine the effect of New Zealand blackcurrant upon functional performance in an

94   aerobic task, while the secondary aims were to examine effects on cognitive function

95   and resting blood pressure in older adults following a 7-day intake.

96   **METHODS**

97   **Participants**

98   Fourteen participants (12 male, age: 69±4 years, height: 172±9 cm, body mass: 85±12

99   kg, BMI: 28.5±2.9) volunteered to participate in the study. Following explanation of

100   the experimental protocol and procedures, potential risks and benefits, participants

101 completed a health history questionnaire and provided written informed consent. The

102 participants were community dwelling, physically active independent older adults, free

103 from any injuries and not taking any prescription medication that controlled blood

104 pressure, heart or neurological conditions. Participants were excluded from the study if

105 they were current smokers or habitually using antioxidant supplements (including

106 vitamin C and E and high anthocyanin products). All participants were also screened

107 for dementia with the Mini-Cog© (3-item recall and clock drawing) and any

108 participants failing the test were not allowed to participate. The study was approved by

109 the University of Worcester Health & Sciences Research Ethics Committee

110 (SH17180001) with protocols and procedures performed in accordance with the ethical

111 principles outlined by the Declaration of Helsinki (World Medical Association, 2013).

112 **Experimental Design**

113 Participants visited the laboratory four times at the same time of day (9:00 or 11:00 am)

114 for each visit. Before arrival, participants were instructed to not consume alcohol the

115 day before and caffeine the day of each visit to the laboratory. Analysis of food diaries

116 indicated 100% adherence to these restrictions. During the first visit participants height

117 (Seca 213, Seca, Birmingham, UK) and body mass (Seca 887, Seca, Birmingham, UK)

118 were measured. Blood pressure was then measured (Omron M5-I, Omron Healthcare

119 Ltd, Milton Keynes, UK) in accordance with methods from the British Hypertension

120 Society. Briefly, participants rested while seated in a chair for 5-minutes before the cuff

121 was placed around the upper arm, with the artery indicator aligned 2cm above the

122 brachial artery. The arm was then rested on a pillow at the level of the heart, with three

123 measures taken and averaged. Subsequently participants completed the cognitive

124 function assessment and 6-minute walk test.

125 The first and second visit allowed familiarisation of the protocols and procedures and

126 were a maximum of 7-days apart (Figure 1 for the timeline of experimental visits). For

127 6-days prior to visits three and four, participants consumed two 300 mg capsules per

128 day of placebo (microcrystalline cellulose M102) or concentrated NZBC extract (300

129 mg containing 105 mg of anthocyanins, i.e. 35–50% delphinidin-3-rutinoside, 5–20%

130 delphinidin-3-glucoside, 30–45% cyanidin-3-rutinoside, 3–10% cyanidin-3-glucoside)

131 (CurraNZ™, Health Currancy Ltd., Surrey, UK). In the first six-days participants were

132 instructed to separate the capsule consumption by an 8-hour interval, while on the

133 morning of the seventh day of intake, participants consumed both capsules 2-hours

134 prior to arriving at the laboratory. The NZBC capsules were independently analysed for

135 ingredients and confirmed the anthocyanin profile. Between visits two and three, there

136 was a 7-day washout, followed by another 7-day intake of the cross over condition

137 capsules. This dosing period has been used previously in studies examining the effects

138 of New Zealand blackcurrant extract on exercise performance and cardiovascular

139 responses.[16,19] Dose response work has also identified 600 mg·day^{-1} (dosed at 300 mg

140 twice daily for 6-days and 600 mg 2-hours before measurement) to alter cardiovascular

141 function with a higher dose having no additional effect.[20]

142   [Insert figure 1 here]

143 **Cognitive Function**

144 Participants completed the Cambridge neuropsychological test automated battery

145 (CANTAB, Cambridge Cognition, Cambridge, UK) to assess cognitive function whilst

146 sat at a desk. The testing battery assessed reaction time, paired associates learning,

147 spatial working memory and rapid visual information processing, and took ~35 minutes

148 to administer on a handheld computer tablet (Gigabyte, Slate S10, Windows 10).

149 Participants were allowed to wear vison correcting eye glasses or contact lenses during

150 the cognitive function assessment. The assessment system has previously been shown

151 to be sensitive to a nutritional intervention of polyphenol supplementation.[21] The

152 battery of cognitive tasks is described in more detail below.

153 Reaction time

154 The reaction time task assessed motor and mental response speeds. The participants

155 held a button at the bottom of the screen and circles were presented above. For the

156 simple reaction mode, a single yellow circle was presented, while in the five choice

157 there were five circles presented with one containing a yellow dot. The participant must

158 release the button at the bottom of the screen and select the circle containing the yellow

159 dot. The test took 3-minutes to administer. The outcome measures included reaction

160 time and movement time for the single and five-choice tests.

161 Paired Associates Learning

162 The PAL test assesses visual memory and new learning taking 8-minutes to administer.

163 Boxes were presented on the screen and some of the boxes randomly revealed a pattern

164 behind them. The patterns were then presented in the order they were revealed, and the

165 participant then had to select the box in which the pattern was originally located. The

166 outcome measures included errors made, the number of trails required to locate the

167 patterns correctly, memory scores and stages completed.

168 Spatial Working Memory

169 The SWM test assessed retention and manipulation of visuospatial information and

170 took 4-minutes to administer. Boxes were displayed on the screen and in a process of

171 elimination participants had to find a yellow token in a number of boxes to fill up an

172 empty column. The test increased in difficulty until 12 boxes were displayed for the

173 participants, and for each trial the colour and position of the boxes changed. Outcome

174 measures included errors of selecting boxes that have already been selected and shown

175 to be empty (working memory) and strategy (indexed strategy of executive function

176 from the number of different boxes participants complete a new search for the token

177 with the same problem).

178 <u>Rapid Visual Information Processing</u>

179 The RVIP test measured sustained attention and took 7-minutes to administer. At the

180 centre of the screen a white box was displayed, wherein numbers from 2-9 appeared in

181 a pseudo-random order at the rate of 100 digits per minutes. Participants were instructed

182 to detect when a target sequence of digits was displayed (i.e. 2-4-6). The outcome

183 measures included were response latency (speed of response), probability of false

184 alarms and sensitivity.

185 **Functional Aerobic Performance**

186 Functional aerobic performance of participants was determined from performance in

187 the 6-minte walk test. Briefly, participants were instructed to walk around a 45.7-metre

188 course (50 yards) as far as they could within 6-minutes. The course was set up indoors

189 on a level non-slip floor with cones marking the walking area. During the 6-minutes,

190 participants were instructed to give their best effort and were given standardised

191 encouragement during the walk. After 6-minutes, total distance covered in metres was

192 recorded.

193 **Physical Activity and Dietary Standardisation**

194 Participants completed a 48-hour food diary before the first and second experimental

195 condition visit (i.e. visit 3 and visit 4). Participant's nutritional intake was not controlled

196 by the study, however at visit three, participants food diary was photocopied to guide

197 them in replicating their intake for the final experimental visits (i.e. visit 4). Participants

198 then recorded their intake for the 48-hours prior to the fourth visit on a new diary. Food

199 diaries were analysed using Nutritics (Nutritics LTD, Dublin, Ireland) for absolute and

200   relative to body mass carbohydrate, fat and protein intake and total energy intake (kJ).

201   The total anthocyanin consumption in the 48-hours before each experimental visits was

202   estimated from the anthocyanin content of food multiplied by the portion size reported.

203   [22]

204   **Statistical Analysis**

205   All data was analysed in SPSS 25.0 (SPSS, Chicago, IL, USA). Data normality

206   assumptions were assessed using Kolmogorov-Smirnov test. Differences between

207   placebo and NZBC conditions were analysed with a paired samples t-tests to compare

208   dietary intake, blood pressure and each parameter of cognitive function and a Wilcoxon

209   Signed Rank test for 6-minute walk performance due to normality violations.

210   Significance was set at alpha level of $P \leq 0.05$. Where differences were present, Cohen's

211   *d* effect sizes were calculated, with an effect size interpreted <0.2 as trivial, 0.2-0.39 as

212   small, 0.4-0.69 as moderate and >0.7 as large.[23] A prior power analysis showed a

213   sample size of 14 would allow detection of a 2-3% difference in exercise performance

214   with an 80% power (1-β=0.80: 0.05=α level).

215   **RESULTS**

216   **Food Diary Analysis**

217   There were no differences (P>0.05) in absolute or relative per kilogram of body mass

218   values for carbohydrate, fat, protein, or total energy for 48 hours prior to each

219   experimental visit (Table 1). The estimated intake of anthocyanins for the 48-hours

220   before the experimental visits was not different (placebo: 84±51; NZBC: 82±52

221   mg·day^{-1}, t=0.839, P=0.416).

222   [Insert table 1 here]

223   **Blood Pressure**

224 Intake of NZBC reduced systolic blood pressure (placebo: 136±14; NZBC: 130±12

225 mmHg, t=2.334, *P*=0.036, *d*=0.46), with a group mean reduction of 5±8 mmHg (range:

226 2 – 22 mmHg) and 10 participants showing a decrease (Figure 2). This was coupled

227 with NZBC also reducing diastolic blood pressure (placebo: 84±11; NZBC 78±6

228 mmHg, t=2.329, *P*=0.036, *d*=0.68), with a group mean reduction of 12±8 mmHg

229 (range: 2 – 23 mmHg) and 8 participants lower (Figure 3).

230 [Insert figure 2 and 3 here]

231 **Cognitive Function**

232 There were no differences in cognitive function variables reaction time, paired

233 associates learning, spatial working memory and rapid visual processing (Table 2)

234 between placebo and NZBC.

235 [Insert tables 2 here]

236 **6-minute walk test performance**

237 Due to balance concerns, one participant did not complete the 6-minute walk test,

238 therefore 13 participants completed and were analysed. There was no difference in total

239 walking distance between the conditions (placebo: 704±72; NZBC: 718±115 metres,

240 *Z*=-0.39, *P*=0.969).

241 **DISCUSSION**

242 The principle finding from this study was that New Zealand blackcurrant extract had a

243 moderate effect on resting systolic and diastolic blood pressure in older adults. Systolic

244 blood pressure was 5±8 mmHg lower and diastolic was 12±8 lower due to the intake of

245 New Zealand blackcurrant extract, with 10 and 8 participants showing a change

246 respectively. However, the study did not confirm our hypothesis of improved functional

247 performance in an aerobic task or cognitive functions by New Zealand blackcurrant

248 extract.

249   To the author's knowledge, this is the first study to demonstrate effects on blood

250   pressure from the intake of New Zealand blackcurrant. Previous studies examining

251   effects of NZBC extract upon cardiovascular responses at rest have shown no effect

252   upon blood pressure in trained cyclists and triathletes.[20,24] Therefore, the results shown

253   in this study may reflect the different participant characteristics between the studies.

254   For example, based upon the resting blood pressure of the placebo condition, 11 of the

255   participants would be classified as having; pre-hypertension with systolic pressure of

256   120-139 mmHg and diastolic pressure of 80-89 mmHg, or hypertension such that

257   systolic was $\geq$140 mmHg or diastolic pressure $\geq$90 mmHg. [25]

258   Recent studies have shown cherry juice to decrease resting systolic and diastolic blood

259   pressure in young and old adults, old adults with mild-to-moderate dementia, middle-

260   aged adults and young men with pre-hypertension.[26–29] Interestingly, the results from

261   these studies both match the methodology within this study such that measurement of

262   blood pressure was taken 2-hours following intake. What is more, it potentially

263   indicates that changes in blood pressure from anthocyanin intake is not specific to

264   cherry but extend to blackcurrant for older adults. Berry specific effects are possible

265   due to the unique anthocyanin profiles within fruits. For example, cherry is high in the

266   anthocyanin cyanidin-3-glucosylrutinoside while blackcurrant is highest in

267   delphinidin-3-rutinoside, which will then have an impact upon the metabolites

268   produced.[22,30] The specific metabolites produced are then determinate of the

269   physiological responses; with Keane et al[31] observing that migration of human vascular

270   smooth muscle cells *in vitro* was dependent upon the presence of both protocatechuic

271   acid and vanillic acid, rather than in isolation.

272   On the whole, the findings in this study may have implications for the management of

273   blood pressure in older adults. For example, blood pressure is a modifiable risk factor

274 for cardiovascular disease, of which, diet is a contributing factor.[32,33] The observed

275 mean decrease in systolic blood pressure of 5 mmHg is meaningful as Collins et al[34]

276 have shown that reductions of 2-5 mmHg can contribute to reductions in cardiovascular

277 mortality. The magnitude of changes in blood pressure in this study are also similar to

278 those of Kent et al.[26] who observed a 5.5 mmHg decrease in both systolic and diastolic

279 blood pressure following cherry juice, and Keane et al[29] who observed a 7±3 mmHg

280 decrease in systolic blood pressure following cherry juice.

281 This study showed no change in cognitive function in older adults following a 7-day

282 intake of anthocyanins from NZBC. These findings reflect those of Keane et al[28] and

283 Bowtell et al[8] who similarly showed no change in cognitive function following cherry

284 juice (measured acutely) and blueberry juice (12-week intake), respectively. However,

285 it contrasts the findings of Watson et al[10] who demonstrated that following

286 supplementation with a single intake of blackcurrant in young adults, digit vigilance

287 was higher, and rapid visual information processing and mental fatigue were lower,

288 with a Bon-Lader visual analogue mood scale also indicating higher alertness in

289 comparison to placebo. These differences may result from methods used to examine

290 cognitive function. Within the current study, cognitive function assessment took ~35

291 minutes to administer and participants completed each test during the battery once.

292 Whereas, the procedure used by Watson et al[10] took 70-minutes and participants

293 completed seven repetitions of the cognitive function tests and in turn, were designed

294 to induce mental fatigue. Furthermore, differences may also occur from duration of

295 intake. For example, Miller et al[35] and Whyte et al[36] both observed positive effects of

296 blueberry anthocyanins on aspects of executive function with a 3 and 6-month intake,

297 respectively. Therefore, the interaction of anthocyanins on cognitive function with and

298 without mental fatigue, and different dosing durations in older adult is potentially an

299 area for future research.

300 This study also observed no change in exercise performance from NZBC in older

301 adults. These findings contrast those of Cook et al[15], Murphy et al[16], Perkins et al[17] and

302 Godwin et al[18] with differences likely due to the ages and training status of the

303 participants and demands of the exercise tests. What is more, the 6-minute walk test

304 used in this study is valid (r=0.78) and reliable (R=0.94 [95% CI 0.90-0.96]) for

305 identifying functional performance limitation in older adults.[37] However, the intensity

306 of the exercise experienced by the participants in this study would likely be low to

307 moderate and the scores of the participants in comparison to normative data are

308 'excellent' as they are within the 90th percentile.[38] As a result, more research is needed

309 to identify if exercise performance is effected in older adults and studies should also

310 examine if functional performance is effected in those with health conditions.

311 As the metabolites produced from different anthocyanin parent bodies are different,

312 future studies with NZBC should examine the time-course changes of NZBC

313 metabolites within plasma and then these can be compared against blood pressure to

314 identify if changes coincide with the peaking of certain metabolites. Furthermore, this

315 is the first study to show changes in resting blood pressure and this occurred in older

316 adults, future investigations should therefore examine cardiovascular function

317 responses during exercise in older adults. The effects of dose and duration of intake on

318 cognitive function should also be addressed, as the findings of this within the literature

319 are unclear. Future studies should also identify if responses to anthocyanin intakes are

320 dependent upon habitual anthocyanin intake. For example, those with a low baseline

321 status of vitamin C and glutathione improved their VO_{2max} following supplementation

322 with vitamin C and N-acetylcysteine, respectively, however the participants with higher

323   baseline levels did not respond. Therefore, similar responses may occur in those who

324   have a low anthocyanin intake. [39,40]

Limitations

326   The results of the present study should not be viewed without recognition for some of

327   the limitations in the study design. Firstly, due the large availability of polyphenols

328   within the diet, there was no dietary restrictions placed upon participants. Polyphenol

329   metabolites can act synergistically, therefore a low polyphenol wash-out diet would

330   confirm the observations were resultant from the NZBC intake. However, this would

331   come with a decrease in ecological validity as any changes are only of interest to

332   practitioners if they can be seen in addition to the normal diet. Secondly, as the testing

333   occurred 2-hours following the last intake of the NZBC extract capsules it is possible

334   that the effects observed on blood pressure are a result of the last intake, rather than the

335   accumulative 7-days intake. As a result of this change in dosing pattern (i.e. 600 mg in

336   one dose on day 7, versus days 1-6 where 300 mg was taken twice) it currently limits

337   interpretation and generalization of the findings. Therefore, future studies should

338   consider this and investigate time-course responses of NZBC intake with a consistent

339   dosing strategy used.

Conclusions

341   In conclusion, a 7-day intake of New Zealand blackcurrant extract can decrease resting

342   systolic and diastolic blood pressure in older adults. There are no effects of 7-days

343   intake of New Zealand blackcurrant upon distance covered during a 6-minute walk test

344   or the cognitive function variables reaction time, paired associates learning, spatial

345   working memory and rapid visual processing in older adults. The implications of these

346   findings are that New Zealand blackcurrant extract could be considered a nutritional

347 strategy to manage resting systolic and diastolic blood pressure in physically active

348 older adults.

349 **Acknowledgement**

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351 Ltd (United Kingdom).

352 **Conflict of interest**

353 The authors declare no conflict of interest.

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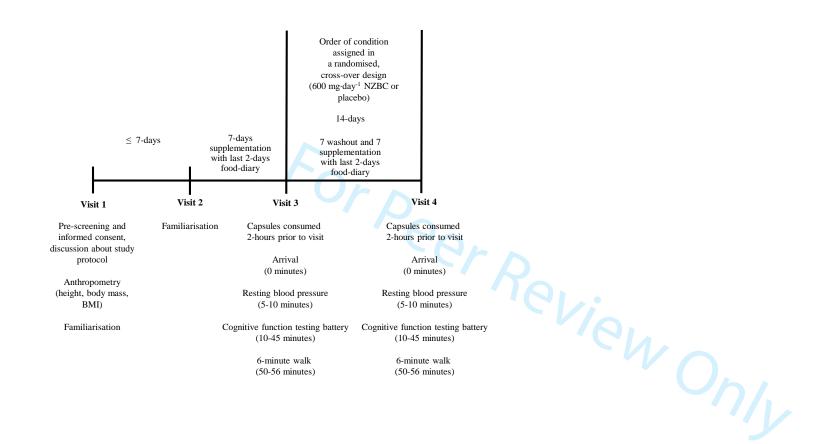
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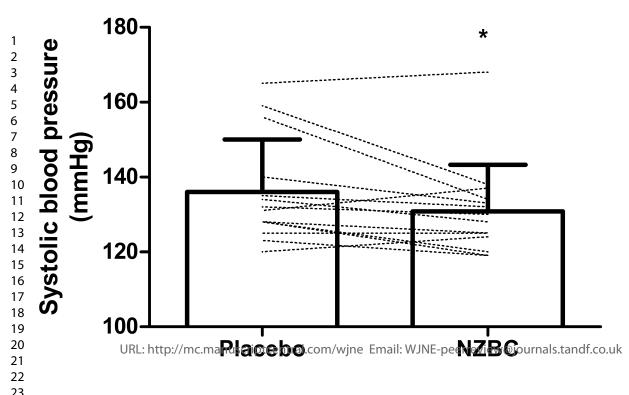471   34.   Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary

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497

FIGURE TITLES

Figure 1 – Experimental design and time line of the four laboratory visits.

Figure 2 – Systolic blood pressure following 7-days intake of New Zealand blackcurrant extract capsules in older adults. Data are mean±SD, * difference between placebo and NZBC extract (P<0.05).

Figure 3 – Diastolic blood pressure following 7-days intake of New Zealand blackcurrant extract capsules in older adults. Data are mean±SD, * difference between placebo and NZBC extract (P<0.05).

Order of condition
assigned in
a randomised,
cross-over design
(600 mg·day⁻¹ NZBC or
placebo)

14-days

≤ 7-days

7-days
supplementation
with last 2-days
food-diary

7 washout and 7
supplementation
with last 2-days
food-diary

Visit 1

Visit 2

Visit 3

Visit 4

Pre-screening and
informed consent,
discussion about study
protocol

Familiarisation

Capsules consumed
2-hours prior to visit

Capsules consumed
2-hours prior to visit

Anthropometry
(height, body mass,
BMI)

Arrival
(0 minutes)

Arrival
(0 minutes)

Resting blood pressure
(5-10 minutes)

Resting blood pressure
(5-10 minutes)

Familiarisation

Cognitive function testing battery
(10-45 minutes)

Cognitive function testing battery
(10-45 minutes)

6-minute walk
(50-56 minutes)

6-minute walk
(50-56 minutes)

Table 1 - Absolute and relative to body mass dietary intake 48 hours before each visit for the experimental conditions.

	Placebo	NZBC
Carbohydrate (g)	404±116	398±106
(g·kg body mass^{-1})	4.8±1.2	4.7±1.2
Fats (g)	143±37	151±48
(g·kg body mass^{-1})	1.7±06	1.8±0.7
Protein (g)	186±13	181±14
(g·kg body mass^{-1})	2.3±0.5	2.2±0.4
Total Energy Intake (kJ)	15,234±1743	15,380±2188
(kJ·body mass^{-1})	184±34	185±35

Values are means±SD, $n = 12$.

Table 2 – Scores for placebo and NZBC on the variables measured for reaction time, paired associated learning, spatial working memory and rapid visual information processing by the Cambridge neuropsychological test automated battery.

	Condition	
	NZBC	Placebo
Reaction Time Variables		
Simple accuracy score (number of correct responses)	29±2	29±1
Simple reaction time (ms)	298±44	301±46
Simple movement time (ms)	192±56	214±76
Five choice reaction time (ms)	327±61	338±58
Five-choice movement time	222±56	250±70
Paired Associated Learning Variables		
Total errors	34±19	24±14
Total errors adjusted (6 shapes adjusted)	11±6	8±5
Spatial Working Memory Variables		
Between errors	15±10	14±8
Strategy	15±8	14±8
Rapid Visual Information Processing		
RVP A	0.93±0.05	0.92±0.07
Probability of hit	0.74±0.16	0.70±0.23
Total false alarms	3.85±5.42	3.67±4.89
Latency (ms)	461±100	482±106

RVP A: Rapid Visual Information Processing detection of signal of target. Values are means±SD, *n* = 14.