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## Effects of *Vaccinium* berries (blueberries, cranberries and bilberries) on oxidative stress, inflammation, exercise performance, and recovery – a systematic review

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Exercise-induced muscle damage is common in athletes and recreational exercisers and can lead to muscle soreness, weakness, and impaired muscle function. The precise mechanisms are unclear but oxidative stress and inflammation are thought to play a role. (Poly)phenols are substances abundant in *Vaccinium* berries that have been suggested to possess antioxidant and anti-inflammatory effects that could help improve exercise performance and/or recovery from exercise. The objective of this systematic review was to evaluate the benefits of *Vaccinium* berry supplementation on exercise performance and recovery, as well as on exercise-induced oxidative and inflammatory biomarkers in healthy individuals. A comprehensive search was conducted in PubMed, ProQuest Medline, Web of Science, Cochrane Library, and Scopus. Studies were included if the participants were healthy individuals who were supplemented with any *Vaccinium* berry or *Vaccinium* berry-based products in comparison to a control group. Of the 13 articles included in this review, no significant differences in the exercise performance were found and only one study reported benefits for markers of recovery. Interleukins and c-reactive protein were the most frequently reported biomarkers, but there was limited evidence that *Vaccinium* berry supplementation impacted them post-exercise. Most studies were of high quality and showed a low risk of bias. *Vaccinium* berry supplementation is not effective in modulating markers of exercise-induced inflammation and oxidative distress in healthy individuals; nevertheless, more studies are required to evaluate their effects on exercise performance and recovery in this population.

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### 1. Introduction

(Poly)phenols are natural compounds that have a variety of potentially beneficial health effects, including antioxidant and

anti-inflammatory activities. They are subdivided into four main classes: flavonoids, phenolic acids, lignans, and stilbenes.<sup>1</sup> (Poly)phenol-rich foods tend to have vibrant bright colours, such as yellow, blue or red, and have a slight acidity, as well as a bitter and sour taste. Fruits such as grapes, apples, pears, cherries, and berries, vegetables such as broccoli, carrots, spinach, and beetroot, and grains such as corn, wheat, oats, and rice all contain high quantities of (poly)phenols. Nevertheless, a variety of other foods like red wine, tea, coffee, chocolate, dry legumes, herbs, spices, stems, and flowers also contain (poly)phenols.<sup>2–4</sup> Various mechanisms have been proposed to explain the antioxidant effects of (poly)phenols: (i) scavenging reactive oxygen and nitrogen species (RONS) production by reducing the catalytic activity of enzymes that participate in the generation of free radicals such as xanthine oxidase;<sup>5</sup> (ii) upregulation of antioxidant defences by activating transcription factors such as nuclear factor erythroid 2-related factor 2 (Nrf2);<sup>6</sup> and (iii) chelation of metal ions and free radicals, preventing their access into cells.<sup>7</sup> While their anti-

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inflammatory effects are related to their antioxidant capacity, (poly)phenols can also downregulate the activity of cyclooxygenase (COX), lipoxygenase (LOX), and nitric oxide synthase (NOS), as well as inhibit tyrosine protein kinase and inflammatory NLRP3 activation, all of which may contribute to the symptoms of exercise-induced muscle damage (EIMD).<sup>8,9</sup>

EIMD is characterised by inflammation, muscle pain (soreness), muscle weakness, and/or impaired muscle function that develops in hours and days after strenuous physical activity.<sup>9</sup> EIMD is especially common in athletes and recreational exercisers after engaging in new or unfamiliar exercise, for example, when learning new techniques or when the intensity or volume of exercise is increased. Several mechanisms of EIMD have been proposed, and inflammation and oxidative stress are thought to play a crucial role in its development. Exercise increases the concentration of key immune cell markers, including several cytokines, white blood cells, and acute phase proteins such as c-reactive protein, in blood and skeletal muscle.<sup>10,11</sup> In addition, several markers of oxidative damage, such as the byproducts of RONS-related damage (e.g., protein carbonyls), and/or markers of redox balance (reduced glutathione/oxidised glutathione), are altered post-exercise.<sup>12,13</sup> Collectively, exercise-induced inflammation and/or oxidative damage is thought to cause secondary damage to muscle and other tissues in the days after strenuous exercise, and this contributes to the muscle pain and/or decrements in muscle function typically observed.<sup>14–18</sup>

(Poly)phenols can also influence endothelial function by increasing the skeletal muscle blood flow.<sup>19,20</sup> This effect is believed to be caused by an increase in nitric oxide (NO) bioavailability, as (poly)phenols inhibit nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an enzyme that reduces NO bioavailability.<sup>19,20</sup> Increased blood flow may improve exercise performance by increasing the supply of nutrients and oxygen to skeletal muscle, as well as by accelerating the clearance of fatiguing metabolites.<sup>19,20</sup>

Berries are among the foods with the highest concentration of (poly)phenols.<sup>21</sup> As such, *Vaccinium* berries may also have the potential to increase physical performance and recovery in athletes, by reducing oxidative and inflammatory-related damage to cells that contribute to EIMD. *Vaccinium* berries, such as blueberries, have been shown to possess comparable antioxidant and anti-inflammatory properties.<sup>22–24</sup> They are easily available to the public and have affordable pricing in comparison to other berries, which makes them attractive to consumers. There are other (poly)phenol-rich berries such as chokeberries (*Aronia melanocarpa*) that have been previously studied as sports supplements,<sup>25</sup> yet they might not be accessible and affordable to most consumers. Elderberries (*Sambucus nigra*) are also known as (poly)phenol-rich berries,<sup>26</sup> yet they have not been studied for any potential sports applications.

Around 60% of the (poly)phenols in fresh blueberries are anthocyanins, with amounts ranging from 93 to 280 mg per 100 g.<sup>27,28</sup> Other (poly)phenols in blueberries include proanthocyanidins, flavonols, and chlorogenic acid.<sup>29,30</sup> *In vitro* findings have shown that blueberry supplementation may

suppress fatigue and oxidative stress-induced muscle damage, as well as oxidative distress in several tissues.<sup>31</sup> They may also accelerate the recovery of muscle peak isometric strength and enhance exercise performance.<sup>32</sup> Since blueberries are low in kilojoules and high in fibre, vitamins C, K, and E, they are also considered healthful foods.<sup>33</sup> Fresh bilberries contain 300 to 698 mg per 100 g of anthocyanins, as well as flavonols, proanthocyanidins, and phenolic acids; they are low in kilojoules and high in fibre and vitamin C.<sup>34</sup> It has been reported that bilberry supplementation might help inhibit smooth muscle contraction and affect vasoactive properties that could increase aerobic exercise performance.<sup>35,36</sup> Additionally, bilberries could also enhance recovery from exercise by inhibiting the expression of pro-inflammatory cells that may contribute to muscle damage.<sup>37–39</sup> Cranberries are low in kilojoules and high in fibre, vitamin C, and a variety of minerals such as manganese, potassium, and magnesium.<sup>40</sup> Raw cranberries are especially rich in anthocyanins and proanthocyanidins, the latter of which might be the main compound responsible for their anti-inflammatory and antioxidant properties.<sup>41</sup> They contain 13.6 to 140 mg per 100 g of anthocyanins,<sup>42</sup> as well as benzoic acid, flavonols, and ursolic acid.<sup>43</sup> Consuming cranberry and cranberry-based products may improve endothelial function, reduce arterial stiffness, attenuate CRP levels, and decrease inflammatory and oxidative distress markers.<sup>44–50</sup>

The aforementioned research with blueberries, cranberries, and bilberries suggests that these *Vaccinium* berries have vasoactive, antioxidant and anti-inflammatory effects and, therefore, the potential to enhance exercise performance and attenuate EIMD. However, studies to date have reported conflicting findings, and there remains no consensus as to the effectiveness of consuming *Vaccinium* berries on exercise performance and recovery in humans. Therefore, in this systematic review, we evaluated studies examining the effects of *Vaccinium* berry supplementation on markers of inflammation, oxidative stress, exercise performance, and recovery in healthy individuals.

## 2. Methodology

This systematic review was pre-registered in the PROSPERO database (ID: CRD42023456233) and was performed according to the recommendations established by the Preferred Reporting Items for Systematic Reviews and meta-Analysis (PRISMA).<sup>51</sup>

### 2.1 Literature search

An extensive search in PubMed, ProQuest Medline, Web of Science, Cochrane Library, and Scopus was conducted on 15th August 2023 to find studies that assessed the effects of *Vaccinium* berry supplementation on exercise performance and recovery in healthy individuals. The search expression consisted of: (*Vaccinium* OR blueberry OR cranberry OR bilberry) AND (exercise OR sport OR athletes OR physically active) AND (antioxidant OR oxidative stress OR inflammatory OR anti-inflammatory OR muscle damage OR recovery OR exercise per-



formance OR sports performance OR performance). Articles relevant to our investigation that were referenced in any of the included studies were also taken into consideration. No limitation was made on the publication date or time length of the studies. The search strategy and inclusion/exclusion criteria based on population, intervention, comparison, outcomes and study design (PICOS) are summarised in Table 1.

## 2.2 Study selection

Included studies were randomized and non-randomized controlled trials in humans that had a control group as a comparator to assess the beneficial effects of *Vaccinium* berry supplementation on markers of exercise performance and recovery. The excluded studies were observational, animal, and *in vitro* studies. Three reviewers independently assessed the titles and abstracts against the inclusion and exclusion criteria. The eligible full-text articles were retrieved. Full-text screening was completed independently by the three reviewers. Any disagreements were resolved through consulting with all the team members by establishing a consensus.

## 2.3 Data extraction

The following data were retrieved from each study: type of intervention, target population characteristics, outcomes, and analysis of these outcomes. All data were summarised and described as qualitative and quantitative variables. A narrative synthesis was performed for the demographic characteristics of the participants such as age, sex, health, and exercise performance activity, the characteristics of the interventions such as dose, frequency, and intervention time of the supplementation with *Vaccinium* berries as well as the characteristics of the placebo, and the assessment tools used to determine the antioxidant, anti-inflammatory, and muscle damage markers, as well as recovery time, quantitative and qualitative exercise performance assessments.

## 2.4 Risk of bias assessment

The scientific quality of the studies was assessed independently by three reviewers using the risk of bias 2 tool (RoB2)

for randomised and crossover trials,<sup>52</sup> and the ROBINS-I tool for non-randomised trials.<sup>53</sup> The assessment of randomised trials was based on the following domains: randomisation process, assignment and adherence to intervention, missing data, measurement of outcome, and selection of the reported results. For crossover studies, the risk of bias arising from period and carryover effects was also considered. For non-randomised studies, the assessment also evaluated the bias due to confounding in addition to the domains stated for randomised studies. The studies were then categorised as having a low risk of bias, some concerns, or a high risk of bias. If assessment outcomes were conflicting, reviewers discussed and came to a consensus. Visualisation of the risk of bias assessments was performed using the *robvis* online tool.<sup>54</sup>

## 3. Results

This systematic review included 13 studies (11 randomised and 2 non-randomised trials). The studies included 9 to 59 participants who were considered healthy and relatively young (18–50 years). Four studies evaluated men only,<sup>55–58</sup> one study evaluated women only,<sup>59</sup> four studies evaluated both,<sup>60–63</sup> and four did not specify gender.<sup>64–67</sup> A total of 287 participants were studied, 58 of which were women and 132 were men; the gender of 98 participants was not disclosed. The studies analysed the effects of supplementation after various types of trials such as running, cycling, jumping, rowing, and using exercise machines. No significant differences in exercise performance were found in any of the studies, and only one study found benefits for strength recovery after exercise.<sup>59</sup> The changes in the relevant biomarkers with each berry are discussed below.

### 3.1 Study selection

The review identified 482 records by searching five databases. After removing duplicates ( $n = 193$ ), 289 articles remained, from which 215 non-clinical trial articles were identified and removed before the screening. 74 articles were then screened

**Table 1** Search strategy and inclusion/exclusion criteria based on population, intervention, comparison, outcomes and study design (PICOS)

Databases	Search terms	PICOS	Inclusion criteria	Exclusion criteria
PubMed, ProQuest Medline, Web of Science, Cochrane, Scopus	<i>(Vaccinium</i> , blueberry, cranberry, or bilberry) AND (exercise, sport, or athletes) AND (antioxidant, “oxidative stress”, inflammatory*, anti-inflammatory*, “muscle damage”, recovery, “exercise performance”, “sports performance”, or performance)	Population	Healthy adults 18 to 65 years old	Unhealthy individuals; individuals below or above the established age range
		Intervention	<i>Vaccinium</i> berry supplementation	Multiple ingredients used as one intervention
		Comparison	Supplementation vs. no supplementation/placebo	
		Outcome	Changes in markers of oxidative stress, inflammatory status, muscle damage, exercise performance and recovery	Alterations in any of the markers before the intervention
		Study design	Randomized, non-randomized, controlled, crossover, and quasi-experimental studies	Meta-analysis, systematic review, cross-sectional, case-control, case reports, animal, and <i>in vitro</i> research studies



by title, abstract, and keywords by all reviewers independently. A total of 61 articles were excluded for different reasons: the study did not evaluate supplementation in humans ( $n = 3$ ); the study targeted sick individuals ( $n = 26$ ); the study did not evaluate markers of inflammation, oxidative stress, exercise performance, or EIMD ( $n = 9$ ); the study evaluated multiple ingredients as a single supplementation ( $n = 13$ ), ongoing clinical trial ( $n = 9$ ), and unclear intervention description ( $n = 1$ ). The excluded study due to unclear intervention description evaluated the effects of blueberry supplementation on exercise performance, total antioxidant status, inflammatory markers and other biomarkers; however, the study did not provide sufficient details regarding the type of supplementation, dosage, total duration of supplementation, nor the (poly) phenol content in its intervention.<sup>68</sup> A total of 13 articles were assessed for eligibility: 10 articles reviewed the effects of blue-

berry supplementation; two studies evaluated the effects of cranberry supplementation, and one study analysed the effects of bilberry supplementation. The details of the study selection process are shown in Fig. 1.

### 3.2 Characteristics of the included studies

**3.2.1 Blueberries.** Among the included studies, three studies were randomised, double-blind, placebo-controlled crossover trials;<sup>61,66,67</sup> three studies were randomised, double-blind, group-controlled parallel intervention trials;<sup>60,64,66</sup> one study was a randomized crossover trial;<sup>59</sup> one study was a randomised, controlled, crossover trial;<sup>63</sup> one study was a non-randomised, group controlled, crossover trial;<sup>55</sup> and one study was a non-randomised, quasi-experimental, free-living trial.<sup>56</sup> The participants of all the studies were healthy adults and this included runners ( $n = 34$ ),<sup>61,66,67</sup> cyclists ( $n = 59$ ),<sup>60</sup> aerobic rec-

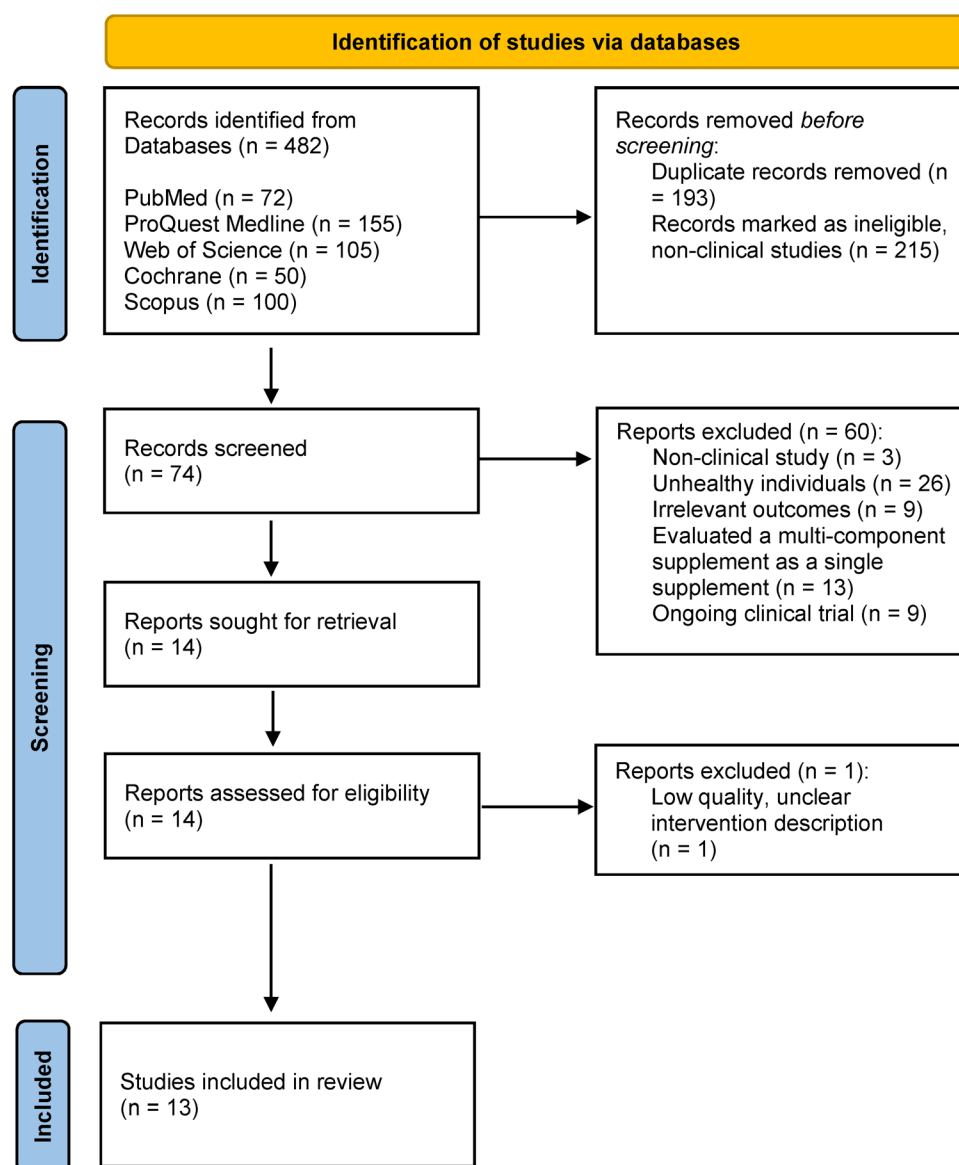


Fig. 1 Preferred reporting items for systematic reviews and Meta-analyses (PRISMA) flow diagram.



reational athletes ( $n = 21$ ),<sup>56,59</sup> trained subjects in running and other forms of aerobic exercise ( $n = 25$ ),<sup>65</sup> and healthy adults ( $n = 86$ ).<sup>55,63,64</sup> The total supplementation duration ranged from two days to eight weeks. Supplementation was given daily in seven of the studies, twice daily in one study, and three times a day in the remaining studies. Five studies used freeze-dried blueberry powder<sup>56,61,64,67</sup> and fresh blueberries were used in the remaining studies.<sup>55,59,60,63,65,66</sup> The dosage in the blueberry powder ranged from 24–72 g per day, while the range varied from 150 to 625 g per day in the studies with fresh blueberries. The details of supplementation used in each study are described in Table 2.

**3.2.2 Cranberries.** Two studies investigated the effect of cranberry supplementation on athletes. One was a double-blind study involving 16 experienced members of the Polish Rowing Team who performed a 2000 m rowing test before supplementation and six weeks after supplementation. Nine members were supplemented with cranberry extract, and the rest were given a placebo. Blood samples were taken before each test, one minute after, and 24 hours later. Total iron-binding capacity (TIBC), unbound iron-binding capacity (UIBC), and total antioxidant capacity (TAC) were determined along with levels of hepcidin, interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), ferritin, iron, and soluble transferrin receptor (sTFR).<sup>57</sup> The other study was a randomised, placebo-controlled, parallel-group intervention that evaluated 20 athlete students majoring in physical education who were supplemented for 14 days and then performed a Bruce-protocol treadmill test. The DNA damage index (DI) was measured through an alkaline comet assay, FPG comet assay, and ENDO III comet assay, along with 8-hydroxy-2-deoxyguanosine (8-OHdG) creatine kinase (CK), blood urea nitrogen (BUN), and malondialdehyde (MDA) plasma levels.<sup>58</sup>

**3.2.3 Bilberries.** One study reviewed the effect of bilberry juice (BJ) supplementation on runners. It was a single-blind, placebo-controlled, parallel-group intervention in which 21 experienced runners were supplemented with either BJ or placebo some days before and after a half-marathon. Muscle soreness assessments and blood samples analysing serum creatine kinase (CK) and C-reactive protein (CRP) levels were collected at baseline, pre-race, and post-race moments.<sup>62</sup>

### 3.3 General findings

**3.3.1 Blueberries.** The review of included studies revealed that blueberries were mostly investigated for their effects on anti-inflammatory, antioxidant, iron metabolism, and muscle damage biomarkers, as well as on exercise performance and recovery.

**3.3.1.1 Effects on oxidative stress and inflammation biomarkers.** The most commonly reported biomarkers were interleukins, especially IL-6, which was reported in five studies. There were no statistically significant differences between the supplementation and control group in any subtype of interleukins.<sup>55,59,61,65</sup> CRP was measured in three studies, none of which reported significant differences between the two groups.<sup>61,63,67</sup> F2-isoprostanes were reported in three

studies, without significant differences between groups.<sup>56,65,66</sup> The ferric-reducing antioxidant potential (FRAP) was measured in three studies,<sup>59,65,66</sup> one of which reported that the assessments of plasma antioxidant capacity between the pre-treatment and the 60-hour recovery time point revealed a significant treatment-in-time interaction for the supplementation group.<sup>59</sup> Manganese superoxide dismutase (Mn-SOD), TNF- $\alpha$ , and DNA damage were analysed in one study, where a significant interaction between pre- and post-intervention over time was reported for Mn-SOD, but no significant changes were reported for the others.<sup>55</sup> Gut phenolic data showed significant group differences in blueberry-related metabolite perturbation between the two groups, as well as significant time per treatment effect in 45 out of 165 gut-derived phenolics, with 24 being associated with blueberry intake.<sup>60</sup> One study reported that 5-hydroxymethyl-2'-deoxyuridine (5-OHMU), a urinary marker of oxidative damage, had a significant decrease post-exercise in the supplemented group, while 8-OHDG did not significantly change.<sup>66</sup>

**3.3.1.2 Effects on muscle damage, exercise performance and recovery.** All three studies that assessed CK levels reported a large rise after exercise, however, no significant between-group differences were found.<sup>59,63,64</sup> Serum troponin-T increased after a running race but there were no significant differences between groups.<sup>63</sup> No significant group differences in creatinine, free/total carnitine, and myoglobin were found.<sup>56,64</sup> Lastly, only one study that assessed exercise performance as isometric, concentric and eccentric torque found a significant reduction at post-exercise and a significantly faster rate of recovery in the blueberry supplementation group.<sup>58</sup> None of the other studies found a significant difference between groups.<sup>55,56,59–61,63–67</sup>

**3.3.1.3 Effects on other outcomes.** Other outcomes include lactate, oxylipins, and natural killer (NK) cells. One study reported that lactate levels were significantly elevated at post-exercise, and higher in the placebo group.<sup>61</sup> In another study, plasma lactate levels were significantly lower in the supplemented group.<sup>64</sup> Lastly, one study reported that lactate levels had a significant interaction between conditions over time at 20, 30, and 40 min post-exercise in the supplemented group.<sup>56</sup> There was a significant increase in plasma levels of arachidonic acid (ARA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in two trials, as well as significant increases in 64 out of 67 identified oxylipins, 15 of which had significant time-for-treatment effects.<sup>56,60</sup> NK cells exhibited significant group, time, and interaction effects in the supplementation group and the mitogen-induced lymphocyte proliferative response decreased post-exercise for both groups in a similar pattern.<sup>63</sup>

**3.3.2 Cranberries.** In one study, there were no significant differences in lactate, myoglobin, IL-6, TNF- $\alpha$ , hepcidin, iron, UIBC, TIBC, sTFR or transferrin levels between the two groups. However, the cranberry extract-supplemented athletes did have significantly higher resting, post-exercise, and post-recovery levels of TAC in comparison to the control group. No significant differences were found in the mean power output



Table 2 Summary of clinical-based trials evaluating the effect of *Vaccinium* berry supplementation on exercise-related outcomes of healthy individuals

Berry	Study	Study design	Participants	Supplemented group	Placebo/control group	Duration	Training load	Key findings
Blueberry	McLeay, Y. <i>et al.</i> , 2011 <sup>59</sup>	Randomized, crossover trial	<i>n</i> = 10 physically active participants Female = 10  Age = 21–23 years	<i>n</i> = 10  Beverage with 200 g of blueberries (96.6 g of ACNs per 100 ml) three times a day for 1 day and once a day for 2 days TAD = 580 mg on the first day, 193 mg for the next days, and 966 mg for full intervention	<i>n</i> = 10  Placebo beverage	3 days	300 maximal eccentric repetitions using the quadriceps	Faster rate of recovery in the blueberry group ( <i>p</i> = 0.047). Faster rate of decrease in oxidative stress was observed in the blueberry group ( <i>p</i> > 0.05)
Blueberry	Brandenburg <i>et al.</i> , 2021 <sup>61</sup>	Randomized double-blind, placebo-controlled, crossover trial	<i>n</i> = 11 physically active participants Male = 4  Female = 7 Age = 20–34 years <i>n</i> = 59 trained cyclists	24 g of blueberry powder (336 mg of ACNs per serving) 3 times a day TAD = 1008 mg per day, 4032 mg for full intervention <i>n</i> = 30	<i>n</i> = 11  Placebo powder	4 days	30-minute run in normobaric hypoxia	Blood lactate was significantly lower in the blueberry group ( <i>p</i> = 0.02)
Blueberry	Nieman, D. <i>et al.</i> , 2020 <sup>60</sup>	Randomized double-blind placebo-controlled, four-group parallel trial	Female = 19 Age = 37–41 years <i>n</i> = 9 physically active participants Male = N/S Female = N/S Age = 18–43 years.	26 g of blueberry powder (345 mg of ACNs per serving) once a day TAD = 345 mg per day, 4830 mg for full intervention <i>n</i> = 9	Carbohydrate and fiber-matched placebo powder <i>n</i> = 9	2 weeks	75-km cycling time trial	Banana and blueberry ingestion were independently associated with significant post-exercise reductions in 10 ARA-CYP pro-inflammatory oxylipins: six HETEs and four diHE/TrEs ( <i>p</i> = 0.003) Significantly lower ROOH concentration in the blueberry group ( <i>p</i> = 0.005)
Blueberry	McAnulty, S. <i>et al.</i> , 2004 <sup>65</sup>	Randomized double-blind, placebo-controlled, crossover trial	<i>n</i> = 14 physically active participants Male = N/S Female = N/S Age = 21–41 years	Session I, 150 g per d of blueberries. Session II, 1250 mg per d vitamin C supplement. TAD = 250 mg per day, and 1750 mg for full intervention. <sup>a</sup> <i>n</i> = 14	Blueberry-flavored shake <i>n</i> = 14	1 week	70% VO <sub>2</sub> max run in a hyperthermic environment until a core temperature of 39.5 °C was reached	There was an interaction effect observed for blood lactate, with lower post-TT concentrations in the 4-day supplementation group ( <i>p</i> = 0.027). A decline in RSI was lower following the 4-day supplementation group.
Blueberry	Brandenburg, J., & Giles, L. 2019 <sup>67</sup>	Randomized, double-blind, placebo-controlled, crossover trial	Female = N/S Age = 21–41 years	24 g of blueberry powder (336 mg of ACNs per serving) 3 times a day. TAD = 1008 mg per day, 4032 mg for 4 days, 2016 mg for 2 days <sup>a</sup> <i>n</i> = 14	Placebo powder <i>n</i> = 14	4 or 2 days	CMVJ, DJ and a 8-km run TT on a non-motorized treadmill	





Table 2 (Contd.)

Berry	Study	Study design	Participants	Supplemented group	Placebo/control group	Duration	Training load	Key findings
Blueberry	McAnulty, L. <i>et al.</i> , 2011 <sup>66</sup>	Randomized, double-blind, parallel-group trial	$n = 25$ physically active participants Male = N/S Female = N/S Age = 18–49 years	$n = 13$ 250 g of fresh blueberries per day and an acute dose of 3.75 g of blueberries within 1 hour before exercise testing. TAD = 491 mg per day, 21 378 mg for full intervention. <sup>a</sup> $n = 11$	$n = 12$ Control group	6 weeks	2.5-hour treadmill run	The blueberry group had significantly lower levels of F2-isoprostanes ( $p = 0.016$ ) and 5-OHMU ( $p = 0.028$ ). IL-10 ( $p = 0.045$ ) and NK cell counts ( $p = 0.003$ ) were significantly higher.
Blueberry	Pirola, K. <i>et al.</i> , 2023 <sup>56</sup>	Non-randomized, quasi-experiment, free-living trial	$n = 11$ physically active participants Male = 11 Age = 18–34 years	12.5 g of blueberry powder twice a day. TAD = 350 mg per day, 4900 mg for full intervention. $n = 23$	"C diet" $n = 26$	2 weeks	65% of $\dot{V}O_{2\max}$ -cycle for 40 minutes	Lactate was lower in the blueberry group ( $p = 0.0053$ )
Blueberry	Nieman, D. <i>et al.</i> , 2023 <sup>64</sup>	Randomized, double-blinded, placebo-controlled, parallel-group trial	$n = 49$ healthy untrained participants.	$n = 23$	$n = 26$	2 weeks	Muscle function tests, 60-yard shuttle run test, and anaerobic power through the 30-s Wingate cycling test. Then a 90-min eccentric exercise.	Linoleic acid oxylipins were lower in the blueberry group ( $p = 0.051$ ). Nine plasma HDoxHes were significantly higher ( $p = 0.008$ ). The composite variables of 14-HDoHE, 17-HDoHE, and the EPA-derived 18-HEPE were significantly higher in the blueberry group ( $p = 0.014$ ). A positive relationship between post-exercise DHA-IOX HDoxHes and SPM intermediates with urine blueberry gut-derived phenolics was found ( $p = 0.023$ and $p = 0.015$ , respectively).
Blueberry	Nyberg, S. <i>et al.</i> , 2013 <sup>63</sup>	Randomized, group controlled, crossover trial	Male = N/S Female = N/S Age = 18–50 years $n = 32$ healthy untrained individuals Male = 15 Female = 17 Age = 21–48 years	25 g of freeze-dried blueberries (280 mg of ACNs per serving) per day, TAD = 280 mg per day, 3920 mg for full intervention $n = 32$	25 g per day of a placebo powder $n = 32$	4 weeks	5-km run at the fastest possible speed at the beginning and end, and a 5-km run per day, 5 times a week	No significant difference in CK, hs-CRP or troponin-T levels between groups



Table 2 (Contd.)

Berry	Study	Study design	Participants	Supplemented group	Placebo/control group	Duration	Training load	Key findings
Blueberry	Bloedon, T <i>et al.</i> , 2015 <sup>55</sup>	Non-randomized, group controlled, crossover trial	<i>n</i> = 10 healthy untrained individuals Male = 10 Age = 21–30 years	<i>n</i> = 10 300 g per d of blueberries. TAD = 600 mg per day, 33600 mg for full intervention. <sup>a</sup>	<i>n</i> = 10 Control group	8 weeks	1-hour treadmill exercise at 70% of their VO <sub>2</sub> max	Plasma MnSOD had a significant interaction between pre- and post-interventions over time ( <i>p</i> ≤ 0.014) in the blueberry group; it also showed a decreasing tendency 30 min after exercise ( <i>p</i> = 0.072). Significantly higher resting, post-exercise, and post-recovery levels of TAC ( <i>p</i> < 0.001) in the cranberry group
Cranberry	Skarpańska Stejnbom <i>et al.</i> , 2017 <sup>57</sup>	Randomized, double-blind, placebo-controlled, parallel-group trial	<i>n</i> = 16 trained rowers Male = 16 Age = 20–22 years	360 mg of cranberry extract (36 mg of PA), per day. TPAD = 36 mg per day, 1512 mg for full intervention.	Dyed gelatin placebo capsules containing “Poznańska” flour <i>n</i> = 7	6 weeks	2000-m test on a rowing ergometer at the beginning and end	
Cranberry	Meihua <i>et al.</i> , 2018 <sup>58</sup>	Randomized, placebo-controlled, parallel-group trial	<i>n</i> = 20 physically active participants Male = 20 Age = 19–22 years	Cranberry soft chews, one daily with a meal 500 mg dried TPAD = 50 mg per day, 700 mg for full intervention. <sup>a</sup>	<i>n</i> = 10 One dextrose capsule a day	2 weeks	Bruce test	Significant increase of DNA DI ( <i>p</i> < 0.01) and 8-OHdG ( <i>p</i> < 0.01) in the control group in comparison with the supplementation group.
Bilberry	Lynn, A. <i>et al.</i> , 2018 <sup>62</sup>	Randomized, single-blind, placebo-controlled, parallel-group trial	<i>n</i> = 21 trained runners. Male = 16 Female = 5 Age = 18–42 years	200 mL of bilberry juice twice a day (≈160 mg/d of ACNs). TAD = 160 mg/day, 1280 for full intervention. <sup>a</sup>	<i>n</i> = 10 200- mL of fruit-flavored maltodextrin powder.	8 days	Half-marathon	Possibly harmful effect (OR 11.6%, 90% CI ± 14.7%) of bilberry juice on DOMS in comparison with placebo. The possibly harmful effect on post-race DOMS was mirrored by a likely harmful effect (OR 0.56, 90% CI ± 0.72) on CRP at 24 h post-race and a possibly harmful effect (OR 0.12, 90% CI ± 0.69) at 48 h post-race.

Abbreviations: 5-OHMU, 5-hydroxymethyl-2'-deoxyuridine; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; ACNs, anthocyanins; ARA-CYP, arachidonic acid cytochrome p450; CI, confidence interval; CK, creatine kinase; CMVJ, countermovement vertical jump; CRP, c reactive protein; DHA-LOX, docosahexaenoic acid and lipoxygenase; diHETEs, dihydroxy-eicosatetraenoic acids; DJ, drop jump; DNA DI, DNA damage index; DOMS, delayed onset muscle soreness; EPA, eicosapentaenoic acid; HDOHE, hydroxy-docosahexaenoic acid; HEPE/HETEs, hydroxy-eicosatetraenoic acids; hs-CRP, high sensitivity CRP; IL, interleukin; MnSOD, manganese superoxide dismutase; N/S, not specified; NK, natural killer; OR, odds ratio; PA, proanthocyanidins; ROOH, lipid hydroperoxides; RSI, reactive strength index; SPM, specialized pro-resolving lipid mediators; TAC, total antioxidant capacity; TAD, total anthocyanin dose; TPAD, total proanthocyanidin dose; TT, treadmill time; and VO<sub>2</sub> max, maximum rate of oxygen consumption.<sup>a</sup> The concentration of TAD/TPAD was estimated using the anthocyanin/proanthocyanidin content reported in other studies.<sup>56,57</sup>



and total row time.<sup>57</sup> In the other study, a cranberry supplementation elicited a significant decrease in various markers of oxidative distress *versus* the control group after exhaustive exercise, however, there were no significant differences in BUN, MDA or CK. Measures of exercise performance or recovery were not evaluated.<sup>58</sup>

**3.3.3 Bilberries.** The one study in the review that used bilberries showed that bilberry juice (BJ) may increase CRP levels and feelings of delayed onset muscle soreness (DOMS) after a half-marathon compared to a placebo. CK levels remained similar throughout the study in both groups. The rise in both

DOMS and CRP might indicate that runners consuming the BJ experienced greater muscle damage during the race than those consuming the placebo. No significant differences were found in the participants' finishing times.<sup>62</sup>

### 3.4 Risk of bias assessment

A total of 11 studies were randomised controlled trials while two were non-randomised trials.<sup>55-67</sup> All but one of the randomised controlled trials was associated with a low risk of bias (Fig. 2 and 3). This one study raised some concerns regarding bias in the randomisation process and deviations from

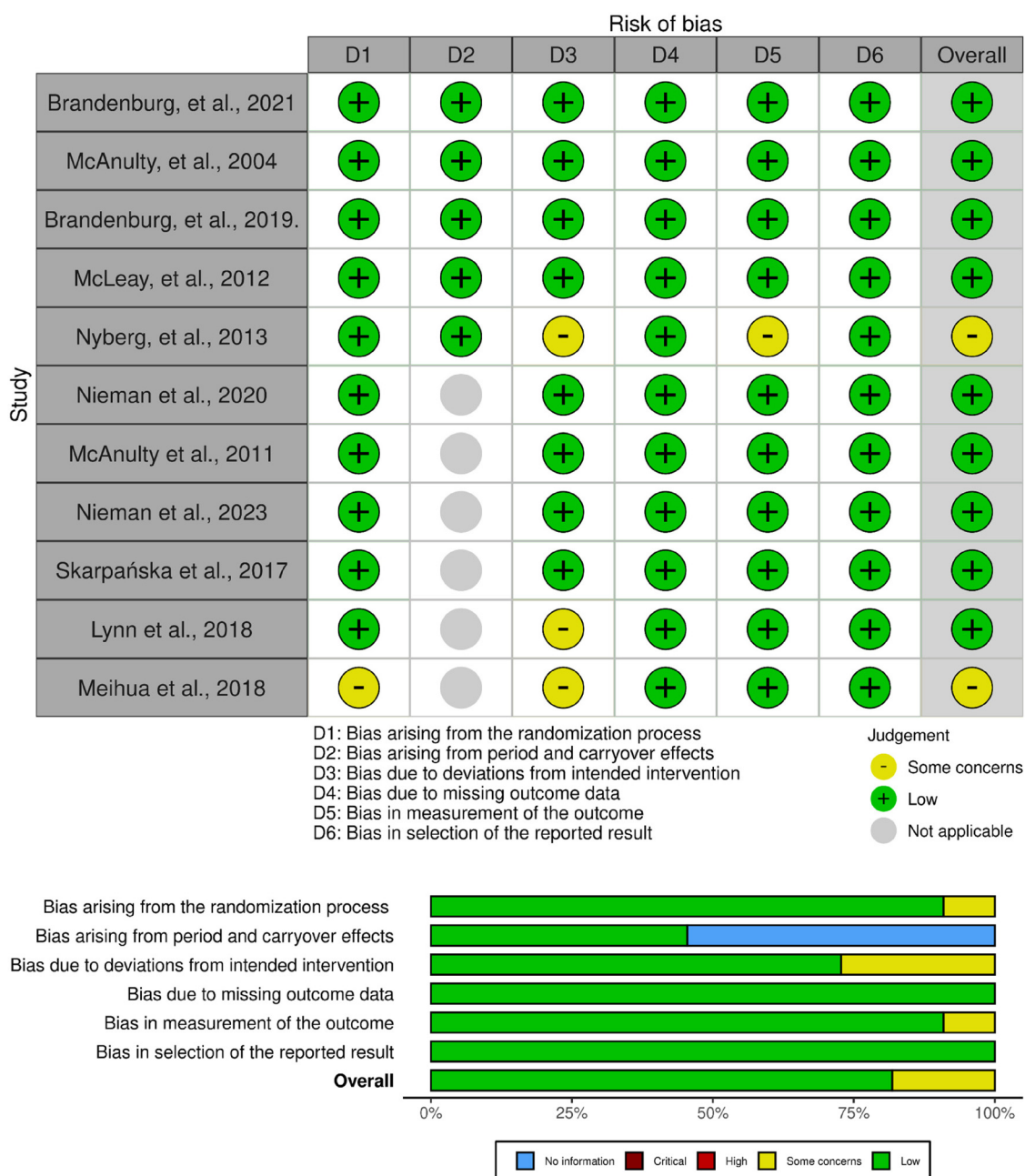


Fig. 2 Assessment of bias of the randomized studies according to the RoB 2 tool: the traffic light plot and summary plot.



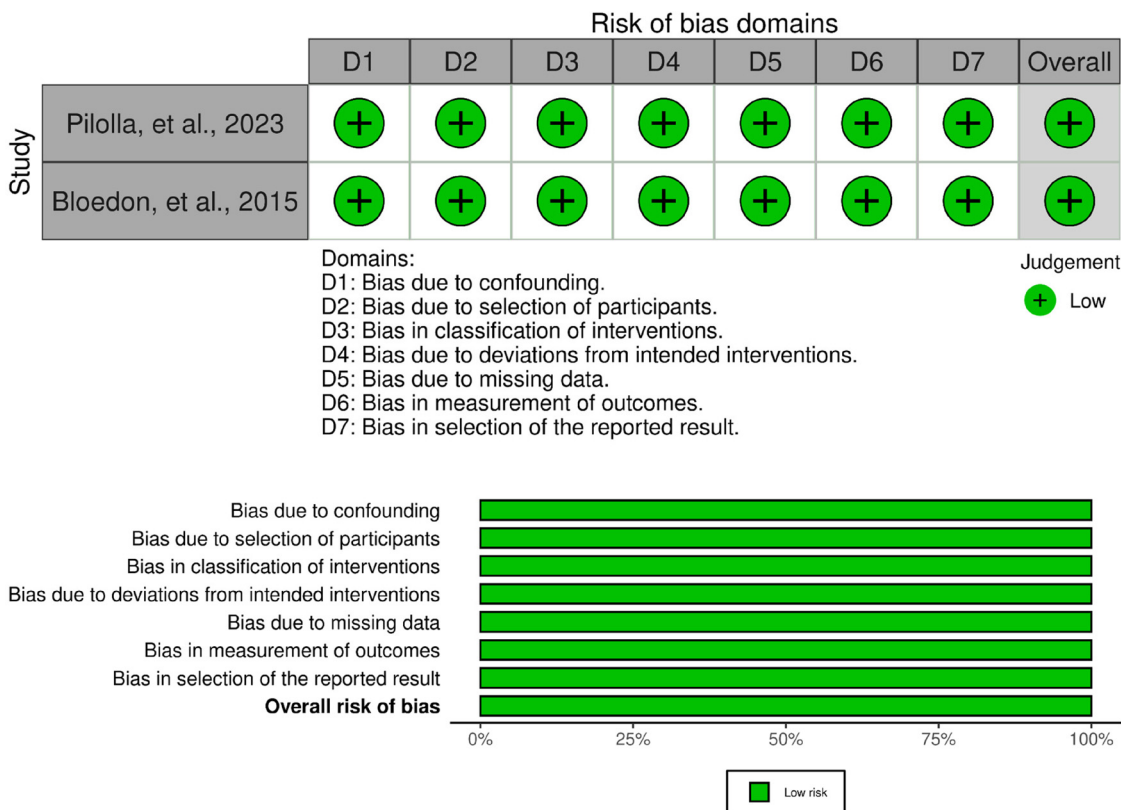


Fig. 3 Assessment of bias of the non-randomised studies according to the ROBINS-I tool: the traffic light plot and summary plot.

intended interventions due to unclear information; however, the baseline difference between intervention groups did not suggest a problem and the deviations were unlikely to affect the outcome.<sup>58</sup> Other than the lack of randomisation, both non-randomised studies were deemed to have a low risk of bias.<sup>55,56</sup> Finally, four out of five crossover studies had a low risk of bias.<sup>59,61,65,67</sup> One study raised some concerns regarding deviations from intended interventions and measurement of outcome; nevertheless, these concerns were deemed not likely to affect the final outcome.<sup>63</sup>

## 4. Discussion

This systematic review evaluated the effect of *Vaccinium* berry supplementation on inflammatory, muscle damage, and oxidative stress biomarkers. We found in most studies *Vaccinium* berry supplementation did not significantly reduce the concentration of these biomarkers. Only one study reported some benefit for strength recovery, and no studies reported significant benefits for exercise performance.

### 4.1 Blueberries

Interleukins were the most frequently measured biomarkers of inflammation in studies evaluating the effects of blueberry intake. However, there were no statistically significant differences between groups, suggesting that the effects of blueber-

ries at that dose, frequency and time of supplementation, were not effective at modulating cytokines. IL-6 was the most frequently measured cytokine; it has been proposed that modulating this cytokine, and other immune cell markers, could help facilitate the recovery of damaged muscle.<sup>69</sup> It has also been reported that the plasma concentration of IL-6 increases during physical activity and peaks post-exercise.<sup>70</sup> The rise in IL-6 may occur in response to muscle damage, however, muscle damage is not required to increase the plasma concentrations of IL-6 during exercise.<sup>71</sup> The main source of IL-6 in response to exercise is skeletal muscle.<sup>69</sup> Additionally, it is believed that the muscle glycogen content is partly responsible for the expression of IL-6 mRNA, so this biomarker is probably more indicative of changes in energy metabolism than muscle damage.<sup>72</sup> Thus, IL-6 is probably not a reliable biomarker to assess post-exercise-induced inflammation, which may partly explain why supplementation had no significant effect on IL-6 levels in most of the studies.

Another biomarker that was frequently measured and that increased post-exercise was F2-isoprostanes, but no significant differences were reported compared to a placebo.<sup>56,65,66</sup> These compounds are produced from arachidonic fatty acids esterified in phospholipids and are released as free isoprostanes by the action of phospholipase A2. F2-isoprostanes cause muscle vasoconstriction, and platelet aggregation, and are considered reasonably good markers of oxidative damage.<sup>73</sup> Since they come from an extravascular origin, short supplementation periods might not



be sufficient to modify these compounds in the extravascular compartment.<sup>74</sup> While the exact consequences of increased F2-isoprostanes are unknown, higher levels are reported after cardiac arrest, in diabetics, and smokers.<sup>66</sup>

The most common muscle damage marker measured in studies with blueberries was CK, an enzyme normally found in skeletal muscle cells but leaks into the circulation after muscle-damaging exercise.<sup>56,59,63</sup> CK levels typically increase post-exercise, which was a common finding in all included studies.<sup>56,59,63</sup> There were no significant differences in CK levels between groups, however, the changes in this biomarker vary greatly between individuals and it has been suggested that this may in part be due to single nucleotide polymorphisms, which may not only limit the efficacy of supplementation, but also the interpretation of post-exercise changes.<sup>56</sup>

Regarding other biomarkers, levels of ARA, DHA and EPA increased significantly after exercise. A correlation between blueberry supplementation and increased intermediate oxylipins generated by DHA and EPA (which have anti-inflammatory effects) was found.<sup>56</sup> The underlying mechanisms are not completely understood, however, it has been suggested that increases in intestinal-derived phenolics and changes in the microbiota caused by the ingestion of (poly)phenols can influence the production of oxylipins through enzymatic stimulation.<sup>75</sup> Likewise, there is a theory that lipid mediators generated from DHA and EPA play a role in muscle regeneration by regulating the inflammatory response.<sup>74,76</sup>

The training status did not appear to affect the effectiveness of blueberry supplementation across the included studies. Three studies with untrained individuals were included, however, most of the investigated biomarkers differed from those reported in other studies, for example, they analysed insulin, triglycerides, HDL-c, and MnSOD; DHA, ARA, EPA, and IL-6 levels were the only variables that were shared between these two groups, showing no significant differences when compared to physically active people.<sup>55,56,63</sup>

#### 4.2 Cranberries

A study in rowers analysed the effect of supplementation on various markers of inflammation and oxidative distress. While there were no statistically significant differences in most of the biomarkers, the lack of post-exercise increases in the supplemented group suggests a possible benefit of cranberry extract components, such as the stimulation of antioxidant capacity and reduction of iron availability *via* chelation.<sup>57</sup> The study in runners evaluated the effect of supplementation on oxidative stress and muscle damage markers.<sup>58</sup> While there were significant differences in oxidative stress markers, the overall description of the intervention and the presentation of the results raised some bias concerns, for example, CK, BUN, and MDA levels of two participants were excluded from the results without explanation.

#### 4.3 Bilberries

A study in runners analysed the effect of supplementation on DOMS, CK and CRP but did not measure any markers of

muscle strength. No benefit was found in exercise performance, recovery or any of the markers. It is also worth noting that the two-day follow-up after the race might not have been enough to fully capture the effects of BJ supplementation on both CRP and CK levels, since both markers had not returned to baseline levels for any of the participants. In addition, there were no diet restrictions in this study, except to avoid NSAIDs and antioxidant vitamins, and this could have influenced the results. Finally, the number of participants in the study was likely insufficient to detect small between-group differences in performance and recovery.<sup>62</sup>

#### 4.4 Limitations and future perspectives

One limitation of this review is the heterogeneity of the studies; indeed, the studies differed considerably, not only in the type of supplementation, administered dose, frequency, and duration of administration, but also in terms of the included participants, (*i.e.*, sedentary individuals in one study, Olympic athletes in the other), as well as the type of physical activity performed. It is perhaps therefore expected that there would be large variation in results between the different studies. While most of the trials reported that oxidative stress, inflammatory status, and muscle damage increased after strenuous physical activity, supplementation did not significantly affect most of these markers.<sup>59,61,65,67</sup> It is also worth noting that, although a small number of studies were included, six out of the thirteen articles were written by the same three authors.<sup>56,59–61,65,67</sup>

We propose several methods to improve research in this area:

(i) studies should ensure that they are sufficiently powered to detect statistically significant group differences by performing *a priori* sample size calculations;

(ii) studies should include measures of exercise performance and recovery, alongside biological markers that interrogate the underpinning mechanisms of action;

(iii) studies should measure the bioavailability of (poly)phenols from consuming these berries. Less than 2% of anthocyanins maintain their original structure after ingestion.<sup>77</sup> Anthocyanins exist in different chemical structures depending on their pH.<sup>77</sup> Additionally, they undergo sulfation, methylation, and enzymatic and microbiota catabolism, which alters their structure producing anthocyanin glucuronides, phenolic acids, and aldehydes.<sup>77</sup> It would be reasonable to assume that any bioactive effects could be related to these metabolites, and not the intact compounds. Nonetheless, only a few studies have evaluated bioavailability alongside their primary outcomes.<sup>49,77–82</sup> Among all of the polyphenols, gallic acid has the highest absorption. Gallic acid, quercetin glucoside, tea catechins, and free hydroxycinnamic acids, which are absorbed in the small intestine and the stomach, reached plasma max concentration ( $C_{\max}$ ) at 1.5 h, whereas rutin, hesperidin, naringin, which are absorbed after the release of the aglycones by the microflora, reached  $C_{\max}$  at 5.5 h. Likewise, the most well-absorbed flavonoids are isoflavones with  $C_{\max}$  values of 2  $\mu\text{mol L}^{-1}$  after a 50 mg intake.<sup>83</sup> When



considering colonic metabolites, the bioavailability of anthocyanins and proanthocyanidins may range from 12% to 18%.<sup>84</sup>

(iv) Among the *Vaccinium* berries included in our systematic review, bilberries are the richest in anthocyanins since they contain 300 to 698 mg per 100 g,<sup>34</sup> while blueberries contain 93 to 280 mg per 100 g,<sup>27,28</sup> and cranberries contain 13.6 to 140 mg per 100 g;<sup>40</sup> therefore, to consume a minimum dose of 80 mg, based on the midrange concentration of anthocyanins in each berry, a minimum of 31 g per d of blueberries, 65 g per d of cranberries, and 16 g per d of bilberries would be required.<sup>85</sup> This recommendation is based on a study in people with risk factors for cardiovascular disease and dyslipidemic subjects, where a dose of  $\geq 80$  mg per d of anthocyanins was effective in lowering inflammation markers such as TNF- $\alpha$ ;<sup>77</sup> regarding cranberries, this amount has a midrange concentration of approximately 76 mg per d of proanthocyanidins,<sup>43,50</sup> more than 1.5 times the amount used in a study in which reduced levels of cholesterol and LDL were observed after supplementation.<sup>77</sup> However, we acknowledge that due to the limited data available on the most efficacious dose of anthocyanins or other (poly)phenols in *Vaccinium* berries, these amounts are only reasonable estimations based on the limited data available.

(v) A minimum wash-out period of 1 week should be used in crossover studies to guarantee that the interventions do not interfere with each other.

(vi) The supplementation period should continue until all relevant plasma biomarkers or exercise performance assessments are expected to return to their baseline levels.

(vii) To gain better mechanistic insights, participants are required to avoid foods/herbs rich in anthocyanins,<sup>83</sup> and other (poly)phenols with similar effects, and avoid the use of medications that are known to affect oxidative stress and immune function.

(viii) No specific or individual biomarkers can validly capture inflammation or oxidative stress, and therefore a wide range of markers should be measured to assess possible effects on these pathways.<sup>84,86</sup> At a minimum, we encourage that the following biomarkers are measured to characterise: (a) inflammation: CRP, TNF- $\alpha$ , interleukin-1b, interleukin-4, interleukin-10 and interleukin-6, as these are key markers from which the Dietary Inflammatory Index was developed, based on their association with food intake; (b) oxidative stress: antioxidants (*e.g.*, glutathione, glutathione peroxidase, catalase, and superoxide dismutase), oxidation products (*e.g.*, protein carbonyls, 8-hydroxyguanosine (8-OHdG), and isoprostanes), and redox balance (*e.g.*, glutathione to oxidised glutathione ratio) (c) muscle damage: CK, LDH, and myoglobin. The wide range of biomarkers employed in the individual studies of this review meant that we were unable to perform a *meta*-analysis in this study.

(ix) We recommend further investigation regarding the effects of bilberry supplementation on exercise performance. Out of the three *Vaccinium* berries, bilberries not only have the highest anthocyanin content,<sup>34</sup> but their effects on exercise performance/recovery have only been examined in one human study.

## 5. Conclusion

Based on the findings from the 13 studies in this review, the results suggest that *Vaccinium* berry supplementation has neither beneficial nor harmful effects on exercise performance or recovery, while the effects on the markers of oxidative stress and inflammation were inconsistent. While most studies had a low risk of bias, many had low sample sizes and did not evaluate the most appropriate outcomes; for example, few studies measured changes in muscle strength following exercise, the most valid marker of EIMD. Future studies are needed to examine whether *Vaccinium* berries can enhance exercise performance and recovery.

## Author contributions

Conceptualisation: A. A. R. and R. Z. Methodology: A. A. R., A. P. M., M. A. C. D., and L. A. R. Investigation, data curation and formal analysis: A. P. M., M. A. C. D., and L. A. R. Writing – original draft: A. P. M., M. A. C. D., and L. A. R. Writing – review & editing: A. A. R., R. Z., S. V. H., K. P., and T. C. Project administration: A. A. R. and A. P. M. Supervision: T. C. and A. A. R.

## Conflicts of interest

All authors declare that they have no conflict of interest relevant to the content of this review.

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