

# THERAPEUTIC REVIEWS

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## Anthocyanosides of *Vaccinium myrtillus* (Bilberry) for Night Vision—A Systematic Review of Placebo-Controlled Trials

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**Abstract.** We have systematically reviewed placebo-controlled trials of *V. myrtillus*-extracted anthocyanosides for evidence of positive effects on night vision. Searches of computerized databases and citations in retrieved articles identified 30 trials with outcome measures relevant to vision in reduced light. Of these, 12 were placebo-controlled. The 4 most recent trials were all randomized controlled trials (RCTs) and were negative in outcome. A fifth RCT and 7 non-randomized controlled trials reported positive effects on outcome measures relevant to night vision. Negative outcome was associated with more rigorous methodology but also with lower dose level and extracts from geographically distinct sources that may differ in anthocyanoside composition. Healthy subjects with normal or above average eyesight were tested in 11 of the 12 trials. The hypothesis that *V. myrtillus* anthocyanosides improves normal night vision is not supported by evidence from rigorous clinical studies. There is a complete absence of rigorous research into the effects of the extract on subjects suffering impaired night vision due to pathological eye conditions. Evidence from methodologically weaker trials and auxiliary evidence from animal studies, trials of synthetic anthocyanosides, and a recent randomized controlled trial of *Ribes nigrum* (black currant) anthocyanosides may warrant further trials of *V. myrtillus* anthocyanosides in subjects with impaired night vision. (*Surv Ophthalmol* 49:38–50, 2004. © 2004 Elsevier Inc. All rights reserved.)

**Key words.** anthocyanosides • bilberry • night vision • systematic review • *Vaccinium myrtillus*

### Background

#### PLANT EXTRACTED ANTHOCYANOSIDES

Anthocyanosides (anthocyanins) are ubiquitous water-soluble glycoside plant pigments evident in the purple coloring of fruits, leaves, and stems. They comprise an anthocyanidin molecule linked to a sugar moiety. Anthocyanidins, of which six are common in plants, are flavonoid compounds with a three-ringed molecular structure.<sup>8</sup> The large number of possible anthocyanidin–sugar combinations and

polymerization of anthocyanosides to form proanthocyanosides (condensed tannins) allows for great variation in the anthocyanoside composition of different plant species.

Anthocyanosides are particularly concentrated in *Vaccinium myrtillus*, a shrub of the Ericaceae family. The species name *V. myrtillus* refers to the bilberry, a low-growing shrub native to Europe and North America, related to, but distinct from varieties of the North American blueberry, *V. corymbosum*.<sup>10</sup> In

*V. myrtillus* the raw fruit contains 0.1–0.25% anthocyanosides by weight and concentrated extracts are standardized to contain 25% anthocyanidins, the equivalent of 37% anthocyanosides.<sup>35</sup> High-performance liquid chromatography of *V. myrtillus* extract separates 15 anthocyanosides representing all the possible combinations of 5 anthocyanidins (cyanidin, delphinidin, peonidin, petunidin, malvidin) with 3 sugar moieties (3-O-arabinosides, 3-O-glucosides, 3-O-galactosides).<sup>31</sup>

## ANTHOCYANOSIDES AND NIGHT VISION

Night vision is important to drivers, pilots, and military personnel as well as to the elderly, the short-sighted, and sufferers of various degenerative eye diseases for whom impaired night vision is often a problem.<sup>42</sup> World War II pilots are said to have eaten bilberry jellies or jams to improve their night vision,<sup>36</sup> and several animal studies suggest a positive effect on dark adaptation. In rats treated with *V. myrtillus* extract, the rods of the retina contained more rhodopsin than those of untreated animals,<sup>24</sup> and faster dark adaptation has been observed in three trials with laboratory animals.<sup>2,13,42</sup>

Possible mechanisms of action on the visual apparatus include accelerated resynthesis of rhodopsin,<sup>1</sup> modulation of retinal enzyme activity,<sup>5</sup> and improved microcirculation.<sup>36</sup> More general effects on vision are claimed for *V. myrtillus* anthocyanosides. In Japan and Korea, bilberry extract is taken to relieve “computer-induced eyestrain,”<sup>26</sup> and the antioxidant activity of anthocyanosides may slow retinal angiopathy that occurs in age-related macular degeneration and diabetic retinopathy.<sup>50</sup>

Although a number of studies conducted since the 1960s suggest that anthocyanoside extracts of *V. myrtillus* improve human vision in reduced light conditions, more recent trials have failed to find such an effect. In view of these contradictory results and continuing claims for efficacy and extensive marketing of bilberry extract, we have systematically reviewed the evidence for and against a positive effect of *V. myrtillus* anthocyanosides on human vision under reduced-light conditions.

## OUTCOME MEASURES

Outcome measures used in many of the trials relate to the rate and extent of dark adaptation, as indicated by a lowered threshold at a given time point, a lowered final threshold, or a shorter time to reach a given threshold value. Thresholds have been determined using various types of apparatus that depend upon a subjective response of the subject. A more objective method has been electroretinographic monitoring of dark adaptation either by measuring

changes in the amplitude of responses to light flashes of constant intensity, or by measuring the intensity of flashes required to obtain electroretinograms of constant amplitude.<sup>40</sup> Rod response within the electroretinogram trace can be isolated by reducing the ambient light and cone response can be isolated by increasing ambient light intensity.<sup>22</sup> The electroretinogram typically has two main peaks. The waveform has an initial negative “a” wave representing the response of the retinal receptors and under mesopic light this wave has two subsidiary peaks representing the cone response ( $a_1$ ) followed by the rod response ( $a_2$ ). The ensuing positive “b” wave represents the response of the bipolar cells and again has a subsidiary cone response ( $b_1$ ) followed by a rod component ( $b_2$ ).<sup>22</sup> Some studies have attempted to control for problematic and transient variations in peak values of the b wave by calculating the ratio  $b_1/b_2$ , based on the assumption that transient variations in both values are proportionate.<sup>41</sup> Point  $\alpha$  has been defined as the point at which this ratio equals one ( $b_1 = b_2$ )<sup>2</sup> and the time taken to reach point  $\alpha$  has been used as a measure of dark-adaptation rate. The studies included in this review recorded electroretinograms by photographing signals displayed on an oscilloscope, and pre-date modern computer signal capture and standardization<sup>30</sup> of testing conditions.

Other studies have measured visual acuity, contrast sensitivity, or critical flicker fusion under reduced light conditions, or have mapped minimum light threshold or visual acuity across the visual field. Recovery of vision after dazzling by bright light has also been assessed, an aspect of night vision which is clearly relevant to drivers.

## Method

Literature searches were made of the MEDLINE, EMBASE, AMED, CINAHL, PsycINFO and CCTR (Cochrane) databases from inception of database to July 2002. The search terms were *bilberry*, *Vaccinium myrtillus*, *Myrtili folium*, *anthocyanosides*, and *vision*. Web sites promoting herbal medicines were searched for references to bilberry, and reference lists of articles retrieved were searched for further trials. Studies in any language were screened against the following inclusion criteria: human subjects, outcome measures relevant to vision in reduced light conditions, and use of a placebo control procedure. Data extraction was carried out by two independent reviewers who resolved differences by discussion. Data extraction from articles in languages other than English was checked by associates who were native or fluent speakers of the language concerned.

Quality of reporting was assessed using the five-point Jadad scale.<sup>23</sup> This is a validated measure of

quality of reporting in which points are awarded if the study is described as randomized (+1); the means of carrying out randomization is described and appropriate (+1); the study is described as double-blind (+1); the means of double-blinding is described and appropriate (+1); and there is a description of withdrawals giving number and reason in both groups (+1). Points are deducted if the method to generate the sequence of randomization is described and is inappropriate (-1); or if the method of double-blinding is described and is inappropriate (-1).

## Results

### OVERVIEW OF LITERATURE SEARCH RESULTS

The searches identified 30 trials testing the effect of *V. myrtillus* anthocyanosides on human vision under reduced light conditions. Many of these trials dated from the 1960s (n = 15), 1970s (n = 3), or 1980s (n = 6); many were not listed in computerized databases and were identified only by searching reference lists of other papers as they were retrieved. The language breakdown of articles was Italian (n = 15), French (n = 8), English (n = 5), German (n = 1), and Brazilian Portuguese (n = 1).

Twelve trials met the inclusion criteria. Of these, five<sup>24,27,32,36,60</sup> were randomized controlled trials (RCTs) and seven<sup>1,4,25,29,40,43,44</sup> were placebo-controlled non-randomized trials. Four of the RCTs,<sup>27,32,36,60</sup> which were also the most recent, showed no positive effects for *V. myrtillus* anthocyanosides on outcome measures relevant to vision in reduced light. The fifth RCT<sup>24</sup> and all seven non-randomized trials reported positive effects of the extract on outcome measures relevant to night vision. Overall, and treating repeat measurements at different time points as a single outcome, the 12 trials made 40 discrete outcome measurements of which 20 were reported as positive. Jadad scores were either 2<sup>32</sup> or 3<sup>27,36,60</sup> for the RCTs with negative outcome, 1 for the positive RCT,<sup>24</sup> and 1 or 2 for the non-randomized trials.

Seventeen trials<sup>5,6,9,11,12,15,16,18–20,33,38,45,48,57–59</sup> of *V. myrtillus* extracted anthocyanosides were excluded because they failed to use a placebo-control procedure. Most used a simple pre-test/post-test design with a single group of subjects. Also excluded was a RCT<sup>7</sup> designed as an equivalence study of procianidol oligomers (polymeric anthocyanosides) of *Vitis vitifera* using *V. myrtillus* extract as the reference treatment. It therefore compared the effect of the same class of organic compound derived from two plant species. It did not, however, use a placebo control and the *V. vitifera* treatment has unknown efficacy. There was, in addition, a recent RCT<sup>37</sup> testing the

effect of black currant (*Ribes nigrum*)–extracted anthocyanosides on dark adaptation, and 13 trials testing the effects of single or synthetic anthocyanosides, either cyanidine<sup>17,21,28,39,41,51–56</sup> or cyanoside chloride.<sup>14,49</sup> The relevance of the auxiliary evidence from these trials is considered in the discussion.

The 12 trials meeting the inclusion criteria are described here in narrative form and are summarized in Tables 1 and 2. They are presented in chronological order, first for the RCTs, and then for the non-randomized controlled trials.

### RANDOMIZED CONTROLLED TRIALS

Jayle randomly assigned 37 healthy young subjects with normal vision to either an acute treatment group or a long-term (7-day) treatment group.<sup>24</sup> Ten subjects from each group were then chosen at random to serve as controls for the opposite treatment. French and English summaries included in the article state that there were 40 rather than 37 subjects, but the discrepancy is not explained. Subjects in the acute treatment group were tested before treatment, then 4 hours and 24 hours after taking four tablets of Pourpranyl. The anthocyanoside content of the tablets is not reported, but contemporaneous literature<sup>59</sup> indicates that each Pourpranyl tablet contained 100 mg *V. myrtillus* extracted anthocyanosides and 5 mg  $\beta$ -carotene. Subjects in the long-term group were tested before and after taking four Pourpranyl tablets per day (two at noon and two in the evening) for 7 days, with post-testing on the morning of the 8th day. Dark-adaptation thresholds measured at eight time points up to 30 minutes were significantly reduced in the experimental group and analysis of variance showed that the average value of the eight points were significantly reduced 4 hours after the acute treatment, and had returned to pre-test values by 24 hours. With the long-term treatment there were no significant differences between pre-test and post-test and dark-adaptation thresholds in control subjects hardly varied between the three test points. Under high mesopic light the macular field of vision was significantly increased (analysis of variance) in size at 4 hours but not at 24 hours or after 8 days of treatment. At low mesopic light levels the central scotoma normally represents 6–7° of arc and vision is impaired because of the high concentration of cones and sparsity of rods in this region. It disappears progressively as the light level is increased. Under high mesopic light the frequency of appearance and density of the central scotoma was significantly reduced (chi-square test) compared to baseline at 4 hours and 24 hours with the acute treatment, and at 8 days with long-term treatment. Under low mesopic light the central scotoma was significantly reduced

TABLE 1

*Summary of Randomized Controlled Trials of Vaccinium myrtillus–extracted Anthocyanosides for Vision in Reduced Light Conditions*

Reference (year) (language)	Design (Jadad Score)	Subjects	Dose: mg anthocyanosides [extract name, manufacturer and additional ingredients]	Outcome Measures and Results
Jayle <sup>24</sup> (1964) (French)	parallel RCT no blinding reported (1)	n = 37 normal vision mean age 32 years	acute dose: 400 mg (n = 18) or placebo (n = 10) long-term: 400 mg/day (n = 19) or placebo (n = 10) for 7 days [Pourpranyl, Chibret: 5 mg β-carotene per 100 mg anthocyanosides]	1. Dark-adaptation threshold at 8 intervals up to 30 min: Lower thresholds & mean threshold at 4h (3.99 vs. 2.55 UL psb.) (p < 0.05), NSD at 24h or day 8 2. Visual field in high mesopic light: larger at 4h (25°14' vs 24°1') (p < 0.05), NSD at 24h or day 8 3. Frequency of appearance & density of central scotoma in high mesopic light: reduced at 4h, 24h, & day 8 (p = ?) 4. Size and density of central scotoma in low mesopic light: smaller at 4h (p = ?) NSD at 24h and day 8; density reduced at 4h, 24h & day 8 (p = ?) 5. Light recognition thresholds for cinematic objects: a) basic shape b) precise identification: more correct responses at 4h (& 24h ?) (p = ?). NSD at 8 days.
Levy <sup>27</sup> (1998) (English)	double-blind crossover RCT 2 week washout (3)	n = 16 healthy males mean age 25 years	Acute doses: 12 mg or 24 mg or 36 mg or placebo [Strix: 2 mg β-carotene per 12 mg anthocyanosides]	1. Full field scotopic retinal threshold: NSD 2. Mesopic contrast sensitivity: NSD 3. Dark-adaptation rate: NSD
Zadok <sup>60</sup> (1999) (English)	double-blind crossover RCT 2 week washout (3)	n = 18 healthy males mean age 26 years	24 mg or 48 mg/day or placebo for 4 days [Strix: 2 mg β-carotene per 12 mg]	1. Full field Scotopic Retinal Threshold: NSD 2. Mesopic Contrast Sensitivity: NSD 3. Dark-adaptation Rate: NSD
Muth <sup>36</sup> (2000) (English)	double-blind crossover RCT 1 month washout (3)	n = 15 male Navy SEALs aged 25–47 years	120 mg/day or placebo for 21 days [US source]	1. Night visual acuity - average & final: NSD 2. Night contrast sensitivity - average & final: NSD
Mayser <sup>32</sup> (2001) (English) Poster	double-blind crossover RCT 28-day washout (2)	n = 119 healthy with normal vision	160 mg/day or placebo for 28 days [Finnish extract]	1. Contrast sensitivity NSD 2. Visual Acuity NSD 3. Final dark-adaptation threshold (mean of last 4 readings) NSD 4. Dark-adaptation rate NSD 5. Time to rod-cone break NSD

RCT = randomized controlled trial; NSD = no significant difference; UL psb = logarithmic unit picostillb.

TABLE 2

Summary of Non-randomized, Placebo-controlled Trials of *Vaccinium myrtillus*-extracted Anthocyanosides for Vision in Reduced Light Conditions

Reference (year) (language)	Design (Jadad Score)	Subjects	Dose: mg anthocyanosides [extract name, manufacturer and additional ingredients]	Outcome Measures and Results
Jayle <sup>25</sup> (1965) (French)	parallel placebo controlled (1)	n = 60 healthy vision aged 20–25 years	acute dose: 600 mg [Medicament Chivret]	<ol style="list-style-type: none"> <li>1. Global retinal light threshold: Decrease at 1h maintained to 2h (p = ?), NSD in controls</li> <li>2. Retinal light threshold at 10 points on the retina: Decrease at 1h maintained to 2h (p = ?)</li> <li>3. Critical Flicker Fusion: NSD pre-post in active or placebo group</li> </ol>
Alferi <sup>1</sup> (1996) (French)	double-blind parallel placebo controlled (2)	n = 12	acute dose: 2,880 mg (n = 6) or placebo (n = 6) [LP 272]	<p>Dark-adaptation curve (ERG):</p> <ol style="list-style-type: none"> <li>1. time to point <math>\alpha</math> reduced ~9min in pre-tests and controls to ~6.5min at 1h and 3h (p &lt; 0.01), NSD 1h to 3h</li> <li>2. Higher values of <math>b_2/b_1</math> at each time point during adaptation up to ~15mins (p = ?)</li> </ol>
Magnasco <sup>29</sup> (1966) (Italian)	crossover placebo controlled (1)	n = 16 normal patients 20–50 years	acute dose (mg?) [Ditta Boselli-SMEA]	<p>Differential mesopic retinal threshold at points 0–180° to the meridian. Pre-post improvements with verum in all subjects: Reduced threshold in foveal and perifoveal regions (n = 3) ~20% (p &lt; 0.01), enlarged mesopic plateau without change in level, (n = 1) 10° nasally, 4° temporally. Global elevation of mesopic plateau, (n = 6) 20–30% increase in sensitivity. Increased sensitivity of the central-pericentral plateau, (n = 6) 20–50% and enlarged plateau 3–13° nasally &amp; 4–10° temporally. NSD in pre-post measures with placebo</p>
Belleoud <sup>4</sup> (1967) French	double blind parallel placebo controlled (2)	n = 40 military pilots	400 mg taken pre-flight or placebo [Difrarel 100: 5 mg $\beta$ -carotene per 100 mg]	<ol style="list-style-type: none"> <li>1. scotopic light threshold: 7 subjects with mediocre initial scotopic threshold (&gt; 0.012 B/hm<sup>2</sup>) improved significantly (p = ?) to <math>\leq</math> 0.12 B/hm<sup>2</sup>, mean change 0.30 B/hm<sup>2</sup>. 13 with initial low threshold showed small changes. 2 control subjects with initial mediocre threshold showed small change (0.125 B/hm<sup>2</sup>). No changes in controls with initial low thresholds</li> <li>2. subjective reports: reduced and shorter-lived post-dazzling after-images, reduced visual fatigue, improved dark adaptation</li> </ol>

TABLE 2  
*Continued*

Reference (year) (language)	Design (Jadad Score)	Subjects	Dose: mg Anthocyanosides [Extract Name, Manufacturer & Additional Ingredients]	Outcome Measures and Results
Ponte <sup>40</sup> (1969) (English)	parallel placebo controlled (1)	n = 30 normal sighted volunteers 17–54 years	600 mg total extract (n = 8) vs. 600 mg total extract with 30 mg β-carotene (n = 12) or placebo (n = 10) [Farmigea, Pisa]	Pre-test day before, 2h and 4h after acute dose. Dark adaptation, ERG up to 16 minutes: faster and higher b wave amplitudes after total extract in 7/8 subjects (p < 0.05 at each timepoint for these 7) at 2h and 4h. No difference 2h vs. 4h. 8/12 subjects faster & augmented b wave after extract + β-carotene: (p < 0.05 up to 9 minutes, trend to 16 minutes). No difference between active treatments (no t-test). NSD pre- to post-test with placebo
Sala <sup>43</sup> (1979) (Italian)	double blind placebo controlled (1)	n = 46 railway night workers normal vision	300 mg/d for 7d (n = 20) or 3d (n = 24) or placebo (n = 20) [source not stated]	1. Dark-adaptation curve (ERG), initial & final thresholds: reduced with verum at 3 and 7 days (p < 0.05). Time to point α: NSD 2. Mesopic light threshold: NSD 3. recovery speed after dazzling: NSD 4. Photochromatic interval for violet: NSD 5. Photochromatic threshold for violet light: lowered (p = ?)
Sbrozzi <sup>44</sup> (1983) (Italian)	parallel placebo controlled (2)	n = 16 outpatients & recovering patients: mean age 29 years	acute: 60 mg (n = 4) or 60 mg/day (n = 6) or placebo (n = 6) for 6 days [Memovisus, Ditta Proter: N-acetylglutamine, & coenzyme B <sub>12</sub> ]	Dark adaptation (ERG): rapid increase in curve b <sub>2</sub> after 6 days of treatment, mean value of point α 8.33 min cf. 12.08 min in placebos (p < 0.001). Acute group: point α 10.75 min at 2 hours (p < 0.05) (4 hours not reported)

NSD = no significant difference; ERG = electroretinogram; B/hm<sup>2</sup> = undefined unit.

in size at 4 hours (analysis of variance) and slightly but non-significantly smaller at 24 hours and at 8 days after active treatment. The density of the central scotoma was reduced significantly at 4 hours, 24 hours, and at 8 days in the active treatment groups (analysis of variance). There were no equivalent changes in central scotoma in the control subjects. Finally, in a cinematic test of adaptation thresholds, dark-adapted subjects were presented with a short film sequence repeated at progressively higher light levels. Threshold light levels were determined at which subjects could first identify the basic shape of an element from the film and then secondly identify the element precisely. There was a statistically significant improvement (statistical test not stated) in thresholds at 4 hours but not at 24 hours or in the long-term treatment group at 8 days. Failure to detect an effect on day 8 after 7 days of treatment is consistent with the time-course of effects suggested by the acute treatment.

In a double-blind crossover RCT with healthy volunteers, Levy found no significant effect of single doses (12 mg, 24 mg or 36 mg) of *V. myrtillus* anthocyanosides containing 2 mg  $\beta$ -carotene per 12 g within 24 hours of treatment on three outcome measures predictive of night time visual performance in pilots.<sup>27</sup> Mesopic contrast sensitivity was defined as the threshold contrast level at which subjects can discern between three possible orientations of illuminated disks of sine-wave gratings of varying frequency. There was no significant difference between treatments in either a mean score for the four different sine-wave frequencies (1.5, 3, 6, 12 cycles/degree) or the individual frequencies. The scotopic retinal threshold was defined as the luminance at which subjects can discriminate a whole-field flickering diffuse white light stimulus presented in a Goldmann–Weekers adaptometer. Dark-adaptation rate was defined as the luminance threshold after 10 minutes of dark adaptation. This is approximately 3 minutes after the rod-cone break during early dark adaptation of the cones. Scotopic retinal threshold and dark-adaptation rate scores were averaged over three tests. Testing was carried out before, then 4, 8, and 24 hours after treatment.

Zadok and the same research group found no significant effect on the same three outcome measures at any timepoint during multiple dosing with the same extract ( $2 \times 12$  mg or  $2 \times 24$  mg/day) for 4 days in a crossover RCT.<sup>60</sup> Subjects were healthy young volunteers with excellent pre-existing night vision. Both references<sup>27,60</sup> from this research group describe the source of the extract as blueberry rather than bilberry but use the species name *V. myrtillus*. The commercial extract used in both studies was Strix, an extract of bilberry.<sup>46</sup>

Muth<sup>36</sup> carried out a crossover RCT with 15 healthy young male naval SEALs to test the effect of 460 mg of concentrated *V. myrtillus* extract (25% anthocyanosides) per day for 21 days on tests of night visual acuity and contrast sensitivity. Both tests were conducted at a scotopic light level in artificially created “full moonlight.” In the visual acuity test subjects were required to determine the orientation of the letter C presented randomly in eight different orientations. The size of the letter was reduced in successive rounds of the test until the subject was unable to correctly determine orientation. The contrast sensitivity test required subjects to discriminate letters of fixed size with varying contrast to their background. There were no significant differences between active and placebo treatments in average visual acuity, final visual acuity, average contrast sensitivity, or final contrast sensitivity, or in non-parametric tests of the number of individual subjects showing improvement in the four measures under the two treatment conditions.

The study by Mayser,<sup>32</sup> reported only as a poster, was a double-blind crossover RCT with a 4-week wash-out period. Healthy subjects ( $n = 119$ ) with no night vision problems, normal dark adaptation, and good visual acuity received either 160 mg of bilberry extract standardized at 25% anthocyanosides per day or undistinguishable placebo for 28 days. Visual acuity and contrast vision were measured at baseline and at the end of each 4-week treatment period. Contrast sensitivity for Landholt-Cs was measured using an Oculus Mesoptometer II and the Frieburg Visus and Contrast Test.<sup>3</sup> Visual acuity for Landholt-Cs was measured using a traditional projector. Final dark-adaptation threshold to green light was measured using dark-adaptation goggles<sup>47</sup> and was taken as the mean of the last four measurements. Contrast vision and visual acuity improved over the four test points for both groups but were not significantly different between groups. The authors attribute the improvement between tests to a learning effect. A sub-analysis of 30 matched pairs of subjects with similar dark-adaptation threshold at the first visit also showed no significant difference between groups after treatment. Nor were there significant differences between groups in dark-adaptation rate or time to reach the cone-rod break.

#### NON-RANDOMIZED PLACEBO-CONTROLLED TRIALS

A second trial by Jayle<sup>25</sup> used a parallel placebo-controlled design but was not randomized. The global light threshold of the retina and at thresholds at 10 discrete points in healthy young male subjects were determined before and then 1 hour and 2

hours after a single 600 mg dose of *V. myrtillus* extracted anthocyanosides. There was a small but statistically significant lowering of the global threshold and in the point thresholds at 1 hour. The effect was greater for the 4 points situated closer to the meridian of the eye ( $6^\circ$ ) than the 6 situated more peripherally ( $15^\circ$ ), but the difference between the two sets of points was not statistically significant. The effect was maintained without further change until 2 hours after treatment. There was no significant difference in critical flicker fusion before and after the active treatment.

In a double-blind placebo-controlled parallel design, Alfieri<sup>1</sup> determined dark-adaptation curves by electroretinography in 12 fasting subjects who were given either 4 tablets each containing 720 mg anthocyanosides or undistinguishable placebos. The electroretinogram was determined using a red filter to aid separation of photopic ( $b_1$ ) and scotopic ( $b_2$ ) traces. The mean time to point  $\alpha$  was improved from approximately 9 minutes to 6.5 minutes in the treated group. The effect on point  $\alpha$  was maintained between 1-hour and 3-hour post-tests with no significant difference between the two tests. Analysis of variance comparing the two post-treatment conditions (1 hour and 3 hour) with pre-test and control values showed this change to be statistically significant. Post-treatment values of  $b_2/b_1$  were higher at each time point during the 15 minutes of dark adaptation monitored.

Magnasco<sup>29</sup> used static perimetry to plot variations in retinal threshold at a series of points in the visual field of 16 normal subjects adapted to mesopic light. In this method the retinal sensitivity at each point is determined by varying the brightness of a test target and finding the threshold brightness at which it can be detected by the subject. Subjects were tested at baseline and 4 hours after treatment with an unreported dose of *V. myrtillus* extract or placebo in a crossover design. Washout period was not reported but placebo and active treatments were given on separate days. A significant lowering of visual threshold or enlargement of the visual plateau was seen in all subjects 4 hours after active treatment. The largest effect was observed in the pericentral area. The trial is not described as randomized or double-blinded.

Belleoud<sup>4</sup> allocated 40 military pilots to two groups each containing 10 jet pilots and 10 helicopter pilots. The study was double-blind but is not described as randomized. Scotopic light threshold after 30 minutes of dark adaptation was measured before and after a night flight. After pre-testing and 4 hours before take-off, subjects were given either two Diffrarel tablets, each containing 100 mg of *V. myrtillus* extracted anthocyanosides, and 5 mg of  $\beta$ -carotene or indistinguishable placebos. They were given two additional tablets 90 minutes before take-off. Night

flights lasted between 1 and 2 hours and subjects were post-tested after landing. The total number of hours flown on the test day varied between subjects from 1 hour to 5.5 hours. An entry requirement for personnel in these squadrons was that their night vision threshold should be  $1.12 \text{ B/hm}^2$  ( $10 \text{ Cd/m}^2$  is the currently recognized value) or less but this threshold varies with fatigue. At pre-test 13 of the pilots in the experimental group had scotopic thresholds categorized as excellent ( $\leq 1.12 \text{ B/hm}^2$ ) and showed only small reductions in threshold at post-test. The seven pilots with mediocre scotopic thresholds at pretest showed significant improvements at post-test with thresholds falling to  $1.12 \text{ B/hm}^2$  or less with an average reduction of  $0.30 \text{ B/hm}^2$  ( $0.18\text{--}0.67 \text{ B/hm}^2$ ). Treatment groups were not balanced for initial scotopic threshold and by chance, 18 of the 20 control subjects had excellent ( $\leq 1.12 \text{ B/hm}^2$ ) pre-test thresholds and showed very little change at post-test. In the 2 control subjects with mediocre pre-test thresholds there was an average reduction at post-test of  $0.13 \text{ B/hm}^2$  ( $0.09\text{--}0.16 \text{ B/hm}^2$ ) but statistical comparison between experimental and control subjects with mediocre pre-test thresholds was considered invalid. A practice effect between pre-test and post-test was observed in both groups but in the experimental group the effect size tended to covary with pretest threshold; subjects with higher pre-test thresholds showed greater reductions at post-test. This relationship did not hold for control subjects. The mean reduction in scotopic threshold between pre-test and post-test for all subjects in the two groups is not reported but was  $0.12 \text{ B/hm}^2$  for experimental subjects and  $0.03 \text{ B/hm}^2$  for controls. An unpaired t-test shows that changes from baseline are significantly greater in the experimental than in the control subjects ( $p < 0.05$ ), but this may be an invalid comparison given the possibility of a ceiling effect in the placebo group. Pilots were also asked to report on the subjective effects of the treatment they received on dazzling, visual fatigue, and adaptation to scotopic light. All experimental subjects reported a reduction in after-image effects caused by dazzling; of the controls, 4 reported a clear improvement, and 6 a slight improvement. All experimental subjects, including 5 who had flown for more than 4 hours that day, reported a reduction in visual fatigue and a slight feeling of euphoria, effects not reported by control subjects. Finally, experimental subjects reported an improvement in their ability to adapt to reduced light.

Ponte<sup>40</sup> used the method of constant stimuli to obtain electroretinograms during dark adaptation in 30 normal volunteers after treatment with 600 mg *V. myrtillus* total extract, 600 mg total *V. myrtillus* extract with 30 mg  $\beta$ -carotene or placebo. The trial used a

parallel design but is not described as randomized. Faster adaptation and augmented values against baseline for the b curve were observed 2 hours and 4 hours after treatment in 7 of 8 subjects who took the total extract, and in 8 of 12 who took extract plus  $\beta$ -carotene. The reported effect was maintained at a similar level from the 2-hour to the 4-hour test and was similar for the two active treatments. The increases in b wave amplitude are reported as statistically significant at each 1-minute interval up to 16 minutes of dark adaptation for the extract-only group and up to 9 minutes in the extract plus  $\beta$ -carotene group but the t-tests were carried out on data only for the subjects showing the positive effect. No significant differences were observed in the placebo group. The authors conclude that the addition of  $\beta$ -carotene made no difference to the dark-adaptation curve, but a statistical comparison of the relevant b curve amplitudes was not made.

Sala carried out a double-blind, placebo-controlled trial in which subjects were given anthocyanosides at 300 mg per day or placebo for either 3 days or 7 days.<sup>43</sup> Subjects were railway workers used to working night shifts. During dark adaptation the initial and final threshold values were significantly reduced relative to baseline after active treatment. This effect was independent of the treatment duration. There was no significant change in the time to point  $\alpha$ , mesopic light threshold or speed of recovery after dazzling. The photochromatic interval is the difference between the level of illumination at which the color of a light disappears (cone threshold) and that at which the light itself disappears (the rod threshold). For violet light, a common color for railway signals, there was no significant effect on the photochromatic interval, but a significant lowering of the absolute photochromatic threshold, at which the color can still be discriminated. The exact design of the trial is not clear from the article. It was probably a parallel design in which 20 subjects received placebo, and of the 26 subjects in the experimental group 24 completed 3 days of treatment and 20 completed 7 days of treatment. The article does not explicitly state that *V. myrtillus* is the source of the anthocyanosides administered but the introduction places the research in the context of earlier *V. myrtillus* trials.

Sbrozzi<sup>44</sup> conducted a double-blind placebo-controlled trial in which outpatients and recovering patients at an ophthalmological clinic were allocated to parallel groups balanced for normal and short-sighted vision. Electroretinograms were recorded during dark-adaptation before and after either a single 60 mg dose or treatment with 60 mg per day for 6 days of *V. myrtillus*-extracted anthocyanosides complexed with N-acetylglutamine and coenzyme B<sub>12</sub> or placebo. After 6 days of active treatment, curve

b<sub>2</sub> recovered significantly more rapidly than in control subjects and the mean time to point  $\alpha$  was 8.33 minutes compared to 12.08 minutes with placebo. Two hours after the acute dose point  $\alpha$  occurred at 10.75 minutes, significantly sooner than in controls. The time to point  $\alpha$  4 hours after the acute treatment is not reported.

## Discussion

### MAIN CONCLUSIONS

Evidence presently available from the most rigorous clinical studies does not support the hypothesis that *V. myrtillus* anthocyanosides improve night vision in healthy subjects. Of the 12 trials meeting the inclusion criteria for this systematic review, 5 are RCTs, 4 of which<sup>27,32,36,60</sup> found no significant effects of *V. myrtillus*-extracted anthocyanosides on vision in reduced-light conditions. The fifth RCT<sup>24</sup> and 7 placebo-controlled, but non-randomized trials, all report positive effects on at least one outcome measure relating to vision in reduced light. The obvious association between methodological rigor, recent publication, and negative outcome is confounded, however, by several factors including dose, possible geographical variations in extract composition, and choice of subject. It should also be noted that methods used to obtain and interpret electroretinograms in the older trials differ from the standardized procedures now used.

### CONFOUNDING FACTORS

#### Dosage

Two of the negative RCTs used relatively low doses of anthocyanosides in acute (36 mg)<sup>27</sup> or short-term ( $\leq 48$  mg for 4 days)<sup>60</sup> treatment regimes. These are the lowest dose levels used in any of the trials. Leaving out the one trial that failed to report dose<sup>29</sup> and assuming a 25% anthocyanoside content in the total extract used in a second trial,<sup>40</sup> acute or daily dose levels, in ascending order, were 12–36 mg,<sup>27</sup> 24–48 mg,<sup>60</sup> 60 mg,<sup>44</sup> 120 mg,<sup>36</sup> 150 mg,<sup>40</sup> 160 mg,<sup>32</sup> 300 mg,<sup>43</sup> 400 mg,<sup>24</sup> 400 mg,<sup>4</sup> 600 mg,<sup>25</sup> and 2,880 mg.<sup>1</sup> The trials with negative outcome correspond to the first, second, fourth, and sixth lowest dose levels, suggesting an association between positive outcome and higher dose levels. Although it may be argued that acute and longer term trials cannot be compared in this way, of the three controlled trials<sup>24,43,44</sup> that compared acute effects with longer term effects, only one<sup>44</sup> suggested that there were cumulative effects in excess of those observed during the first few hours after treatment. Of note is the exceptionally high acute dose of 2,880 in one trial.<sup>1</sup> Even if this actually refers to total extract with a 25% anthocyanoside content, the resulting dose of 720 mg is

still higher than any of the other studies. A general cautionary note should perhaps be sounded regarding the interpretation of reported *V. myrtillus* anthocyanoside content of treatments in the older trials, where it is not clear how the extracts have been standardized.

### Phytochemical Composition

As a commercial crop *V. myrtillus* has been subject to deliberate selection for desirable agricultural characters as well as natural selection in a variety of soils and climates. Geographic and cultivar (crop variety) variation in the phytochemical composition of the fruit is therefore likely<sup>10</sup> and may also be relevant to the conflicting outcomes of these trials. High performance liquid chromatography analysis of 30 samples of *V. myrtillus* from different parts of Europe distinguished the anthocyanoside composition of fruits from Norway and Sweden from those of Italy, Poland, and Romania, with fruits from France being intermediate in composition.<sup>31</sup> These were differences in the relative content of different anthocyanosides. The two RCTs<sup>27,60</sup> using the lowest dose and reporting a negative outcome both used Strix tablets, an anthocyanoside extract of the Swedish bilberry *V. myrtillus* var. *fructus*.<sup>60</sup>

Of the other two negative trials, one<sup>32</sup> used a non-commercially available extract thought to be from Finnish bilberries (personal communication, H. Mayser) and the other<sup>36</sup> carried out in Florida obtained the extract from the American branch of an Italian company, Indena USA (personal communication, E. Muth). Of the 8 trials reporting a positive outcome, 3 used an Italian-produced extract,<sup>29,40,44</sup> 4 a French-produced extract,<sup>1,4,24,25</sup> and the source of the other cannot be determined but was probably Italian.<sup>43</sup> These trials were carried out in France or Italy, are older, and the extracts are likely to have used locally grown fruit. Positive outcome may therefore be associated with trials using French or Italian sourced extracts. Like plant secondary metabolites in general, anthocyanoside content varies during the life cycle of the plant and in response to environmental cues and stressors. For example, the anthocyanoside content of *V. myrtillus* increases and the proanthocyanidin content decreases during ripening.<sup>34</sup> Such variations along with geographical differences mean that standardization of anthocyanoside content at a fixed percentage of the extract is an insufficient procedure to ensure identical composition or pharmacological activity.

### Additional Ingredients

Several trials used anthocyanoside treatment with one or more additives.  $\beta$ -carotene was a component

of the active treatment in 5 of the trials.<sup>4,24,27,40,60</sup> It is also explicitly reported as a component in some of the uncontrolled trials excluded from this review.  $\beta$ -carotene is a plant-derived precursor of vitamin A and its deficiency is known to be associated with impaired night vision.<sup>15</sup> The confounding effect of  $\beta$ -carotene on the outcome of these trials cannot therefore be adequately assessed without knowing the nutritional status of the subjects. One study<sup>40</sup> included in this review reports no difference in the electroretinograms of subjects treated with *V. myrtillus* extract with and without  $\beta$ -carotene and cites 3 studies from the 1940s which purportedly show that  $\beta$ -carotene has no effect on dark adaptation when administered alone. The likely contribution to reported positive effects of the additives acetylglutamine and coenzyme B<sub>12</sub> in one trial<sup>44</sup> cannot be assessed.

### Choice of Subjects

A ceiling effect in subjects with good pre-existing night vision may have influenced the outcome of trials included in this review. One of the negative trials<sup>36</sup> used long-term (21 days) treatment with 120 mg anthocyanosides per day but the subjects were healthy young Navy SEALs with largely good night vision, and two further negative trials<sup>27,60</sup> used outcome measures relevant to night marksmanship in military personnel. The level of performance required for good night marksmanship could be viewed as lying at the extreme end of a normal distribution. Because of earlier findings that *V. myrtillus* derived improvements in night vision in military pilots were restricted to subjects with initially mediocre scotopic light thresholds,<sup>4</sup> the authors of the more recent trial<sup>36</sup> specifically examined the performances of two subjects with below-average scotopic visual acuity and contrast sensitivity and found that they showed no improvement after treatment. The two trials used similar populations but the comparability of “below-average” performance in two outcome measures for Navy SEALs with “mediocre” performance in a third measure for military pilots, and with the night vision of the general population remains unknown. Furthermore, below average performance is not the same as suffering an abnormal condition and conclusions about the therapeutic value of *V. myrtillus* in abnormal eye conditions cannot be drawn from these studies.

It should be noted that positive effects are reported with healthy subjects in 5 of the other trials,<sup>24,25,29,40,43</sup> including one RCT.<sup>24</sup> An additional trial<sup>1</sup> reporting positive effects describes its subjects only as human but they probably had normal vision. The population studied by Sbrozzi<sup>44</sup> were ambulatory and recovering

patients of an eye clinic but the nature of their ailments or treatments is not described, only that 8 were myopic and 8 emmetropic. It may be relevant that this trial observed a rather large effect after 6 days treatment with a relatively low daily dose of 60 mg per day. It is notable that despite claims that *V. myrtillus* anthocyanosides are an effective treatment for poor night vision, there has not been a single placebo-controlled trial, randomized or otherwise, which has specifically set out to test this hypothesis.

#### AUXILIARY EVIDENCE

There are several sources of evidence, auxiliary to this systematic review, that should be considered. First is a recent double-blind crossover RCT<sup>37</sup> that tested the effect of *Ribes nigrum* (black currant) anthocyanosides on dark adaptation. A statistically significant lowering of dark-adaptation threshold at 30 minutes was observed in 12 healthy subjects after a single 50-mg dose of extract. A dose-dependent effect is suggested by a similar trend seen at lower doses (12.5 mg and 20 mg). *R. nigrum* has a relatively simple anthocyanoside content comprising only four components, and high-performance liquid chromatography analysis shows that two of these (delphinidin 3 glycoside and cyanidin 3 glycoside) are major components of the more complex anthocyanoside content of *V. myrtillus* extracts.<sup>37</sup> Additionally, a synthetic cyanidin-based anthocyanoside was the subject of a number of placebo-controlled trials<sup>17,21,28,39,41,51–56</sup> carried out during the 1970s and 1980s, which collectively indicate positive effects on night vision in healthy subjects and patients suffering from a variety of ophthalmological disorders. Sixteen uncontrolled trials of *V. myrtillus* anthocyanosides were excluded from this review and found positive effects on measures relevant to night vision in either healthy subjects or patients with a range of visual disorders. Only one uncontrolled trial<sup>48</sup> was negative in outcome and no conclusions regarding efficacy of *V. myrtillus* could be drawn from the excluded equivalence study.<sup>7</sup> The results of uncontrolled trials are of questionable value because positive outcomes may be the result of a placebo effect, and simple pre–post designs with a single experimental group do not incorporate a blinding procedure for experimenters. Dark-adaptation measures that depend on the subjective responses of subjects may be particularly susceptible to placebo effects.

Nevertheless, taken together, the evidence from uncontrolled trials of *V. myrtillus* anthocyanosides, the evidence from controlled trials of related synthetic anthocyanosides, RCT evidence from the *R. nigrum* study<sup>37</sup> and evidence from animal studies<sup>2,13,24,42</sup>

constitutes a sizeable body of positive auxiliary evidence to be considered before dismissing completely the potential therapeutic role of *V. myrtillus* anthocyanosides.

#### SAFETY

Extracts of *V. myrtillus* appear to be well tolerated in toxicity studies with dogs and rodents, and no adverse effects have been reported in any of the trials, or a post-marketing surveillance study (n = 2,295).<sup>34</sup> Of the 2,295 participants, 94 complained of side effects that were mainly gastro-intestinal, or related to the skin or nervous system.

#### PROBLEMS AND LIMITATIONS OF THE REVIEW

Several problems were encountered while carrying out this review. The first was that many of the older references are not listed in any of the computerized databases searched and were identified only from citations in other articles. It may mean that we have not identified all of the uncontrolled trials of *V. myrtillus* and the references for trials of synthetic anthocyanosides may not be complete. It may be that positive publication bias was more prevalent when many of the earlier trials were carried out and there is also a danger of positive citation bias. The combination of poor reporting and reporting in non-English languages made some of the data difficult to extract, and in a few cases even with the help of native speakers trained in ophthalmology, certain measuring procedures remained obscure. However, this has not prevented extraction of the main design features and outcomes of the trials.

#### Future Research

Given the confounding factors discussed above and the evidence from older though somewhat less rigorous trials, and from the auxiliary sources discussed above, further trials of the efficacy of *V. myrtillus* extracts specifically for people complaining of poor night vision may be warranted. Uncontrolled trials report a beneficial effect of the extract on patients suffering tapeto-retinal degeneration,<sup>19,61</sup> myopia,<sup>7,12,16,58</sup> simple glaucoma,<sup>11,12</sup> and pathological fundus.<sup>57</sup> Trials of synthetic anthocyanosides suggest positive effects upon myopia,<sup>14,17,49,51,56</sup> central retinal lesions,<sup>39</sup> and night blindness.<sup>49</sup> The extract is also widely prescribed for diabetic retinopathy.<sup>35</sup>

It may be of interest to re-examine the effects of *V. myrtillus* anthocyanosides extracted from Southern European sources and to investigate whether high levels of particular anthocyanoside components are associated with positive outcome. Modern, standardized ophthalmological measures of dark adaptation

and scotopic and mesopic visual sensitivity and acuity, which can differentiate healthy subjects from those complaining of poor night vision, should be used.

### Method of Literature Search

Literature searches were made of the MEDLINE, EMBASE, AMED, CINAHL, PsycINFO, and CCTR (Cochrane) databases from inception of database to July 2002. The search terms were *bilberry*, *Vaccinium myrtillus*, *Myrtilli folium*, *anthocyanosides*, and *vision*. Web sites promoting herbal medicines were searched for references to bilberry, and reference lists of articles retrieved were searched for further trials. Studies in any language were screened against the following inclusion criteria: human subjects, outcome measures relevant to vision in reduced light conditions, and use of a placebo control procedure. Data extraction from articles in languages other than English was checked by associates who were native or fluent speakers of the language concerned. Also referenced are articles referred to in the text which are relevant to the background of this research, interpretation of the results, or the recommendations for future research.

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