# An Evidence-Based Systematic Review of Bilberry ( Vaccinium myrtillus ) by the Natural Standard Research Collaboration

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# An Evidence-Based Systematic Review of Bilberry (*Vaccinium myrtillus*) by the Natural Standard Research Collaboration

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**ABSTRACT.** An evidence-based systematic review including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

**KEYWORDS.** Adverse effects, bilberry (*Vaccinium myrtillus*), dosing, evidence-based, interactions, pharmacodynamics, pharmacology, pharmacokinetics, systematic review

## *SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE*

### *Search Strategy*

To prepare each Natural Standard review, electronic searches are conducted in nine databases, including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT. Search terms include the common name(s), scientific name(s), and all listed synonyms for each topic. Hand searches are conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions are placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) are consulted for access to additional references or ongoing research.

### *Selection Criteria*

All literature is collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria are utilized for selection.

### *Data Analysis*

Data extraction and analysis are performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertain to each review section (defining

inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data are verified by a second reviewer.

### *Review Process*

A blinded review is conducted by multidisciplinary research–clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addresses conflicts, and consults experts when applicable. Authors of studies are contacted when clarification is required.

### *Synonyms/Common Names/Related Substances*

- Airelle, anthocyanins, Bickbeere (German), bilberry leaf, black whortle, Blaubeere (Dutch), blaubessen, bleaberry, blueberry, blueberry leaf, bogberry, bog bilberry, burren myrtle, cranberry, dwarf bilberry, dyeberry, Ericaceae (family), European blueberry, Heidelbeere (Dutch), Heidelbeereblatter, heidelberry, huckleberry, hurtleberry, lingonberry, lowbush blueberry, *Mirtillo nero* (Italian), *Myrtilli folium*, *Myrtilli fructus*, *Myrtilus niger* Gilib., Optiberry, resveratrol, sambubiosides, trackleberry, *Vaccinium angulosum* Dulac, *Vaccinium montanum* Salibs., *Vaccinium myrtillus* anthocyanoside extract, VMA extract, VME, whortleberry, wineberry.

## *CLINICAL BOTTOM/EFFECTIVENESS*

### *Brief Background*

- Bilberry, a close relative of blueberry, has a long history of medicinal use. The dried fruit has been popular for the symptomatic treatment of diarrhea, for topical relief of minor mucus membrane inflammation, and for a variety of eye disorders, including poor night vision, eyestrain, and myopia. Bilberry is also commonly used to make jams, pies, cobblers, syrups, and alcoholic/nonalcoholic beverages. Fruit extracts are also used as coloring agents in wines.

- Bilberry fruit and its extracts contain a number of biologically active components, including a class of compounds called anthocyanosides, which have been the focus of recent research in Europe.
- Bilberry extract has been evaluated for its efficacy as an antioxidant, mucostimulant, hypoglycemic, antiinflammatory, vasoprotectant, and lipid-lowering agent. Although preclinical studies have been promising, human data are limited and largely of poor quality. At this time, there is insufficient clinical evidence in support of (or against) the use of bilberry for most indications. Notably, the available evidence suggests a possible lack of benefit of bilberry for the improvement of night vision.

### *Scientific Evidence for Common/Studied Uses*

| Indication | Evidence grade |
|---|---|
| Atherosclerosis and peripheral vascular disease | C |
| Cataracts | C |
| Chronic venous insufficiency (CVI) | C |
| Diabetes mellitus | C |
| Diarrhea | C |
| Dysmenorrhea | C |
| Fibrocystic breast disease | C |
| Glaucoma | C |
| Peptic ulcer disease (PUD) | C |
| Retinopathy (diabetic, vascular) | C |
| Night vision | D |

### *Natural Standard evidence-based validated grading rationale™*

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and folkloric precedent are not included in this assessment, and are reflected in a separate section of each review ("Strength of Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

| Level of evidence grade | Criteria |
|---|---|
| A (strong scientific evidence) | Statistically significant evidence of benefit from >2 properly randomized control trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory. |
| B (good scientific evidence) | Statistically significant evidence of benefit from 1 to 2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND with supporting evidence in basic science, animal studies, or theory. |
| C (unclear or conflicting scientific evidence) | Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,[a] OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory. |
| D (fair negative scientific evidence) | Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/ nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit. |
| F (strong negative scientific evidence) | Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.[a] |
| Lack of evidence[b] | Unable to evaluate efficacy due to lack of adequate available human data. |

[a]Objective criteria are derived from validated instruments for evaluating study quality, including the five-point scale developed by Jadad et al. (1996), in which a score below 4 is considered to indicate lesser quality methodologically.
[b]Listed separately in reviews in the "Historical or Theoretical Uses which Lack Sufficient Evidence" section.

## *Historical or Theoretical Uses Which Lack Sufficient Evidence*

- Age-related macular degeneration, angina, angiogenesis, antifungal, antimicrobial, antioxidant (Laplaud, Lelubre, & Chapman, 1997; Martin-Aragon et al., 1998, 1999; Prior et al., 1998), antiseptic, antiviral,

arthritis, astringent, bleeding gums, burns, cancer (Bomser, Madhavi, Singletary, & Smith, 1996; Katsube, Iwashita, Tsushida, Yamaki, & Kobori, 2003; Zhao, Giusti, Malik, Moyer, & Magnuson, 2004), cardiovascular disease, chronic fatigue syndrome, common cold, cough, dermatitis, dysentery, dyspepsia, edema, encephalitis (tick-borne) (Fokina, Roikhel, Frolova, Frolova, & Pogodina, 1993), fevers, gout, hematuria, hemorrhoids (Morazzoni & Magistretti, 1986; Oliva et al., 1990; Pezzangora et al., 1984), hyperlipidemia (Cignarella, Nastasi, Cavalli, & Puglisi, 1996; Laplaud et al., 1997; Rasetti et al., 1997; Viana et al., 1996), hypertension, infantile dyspepsia, kidney disease, lactation suppression, (Magistretti, Conti, & Cristoni, 1988), laxative (fresh berries), leukemia, liver disease, macular degeneration, nephrolithiasis, oral ulcers, pharyngitis, poor circulation, retinitis pigmentosa (Caselli, 1985; Cluzel, Bastide, Wegman, & Tronche, 1970; Fiorini, Biancacci, & Graziano, 1965), scurvy, skin infections, sore throat, tonic, urinary tract infections, varicose veins of pregnancy (Grismondi, 1981), vision (myopia) (Caselli, 1985; Grosse-Ruyken, 1977; Politzer, 1977), wound healing.

### *Expert Opinion and Historic Precedent*

- Currently, bilberry products are used in Europe as vasoprotective agents. They have also been used to prevent or treat various disorders of the eye, especially night blindness. In addition, bilberry has been used to treat eye conditions, such as cataracts, diabetic retinopathy, retinitis pigmentosa, glaucoma, and macular degeneration.
- Herbalists have used bilberry to treat diarrhea and a bilberry leaf extract to treat urinary tract infections. Some surgeons in Europe recommend bilberry for enhanced wound healing. According to secondary sources, bilberry's tannin content may account for its historical use as a treatment for diarrhea, oral ulcers, and sore throats; however, there is a lack of available confirmatory studies.
- Secondary sources have noted that the use of bilberry leaf extracts in high doses is often regarded as unsafe due to potential toxic side effects.

### *Brief Safety Summary*

- *Likely safe*: When consumed in amounts typically found in foods or as a fruit extract in recommended doses by otherwise healthy individuals for brief periods of time.

- *Possibly unsafe*: When used in patients with disorders of platelet function, bleeding disorders, or if taking oral anticoagulant therapy, due to an increased risk of bleeding (theoretical) (Bottecchia, 1987; Fdez, Zaragoza, & Alvarez, 1983; Morazzoni & Bombardelli, 1996; Pulliero et al., 1989; Zaragoza, Iglesias, & Benedi, 1985). When used in combination with hypoglycemic medications, due to an increased risk of hypoglycemia (theoretical) (Allen, 1927; Bever, 1979; Cignarella et al. 1996).
- *Likely unsafe*: When used in large quantities, due to potential acute toxicity that may occur in the form of hydroquinone poisoning, anticoagulation, or gastrointestinal distress (Havsteen, 1983).

## *DOSING/TOXICOLOGY*

### *General*

- Recommended doses are based on those most commonly used in available trials or in historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active components of a product are, standardization may not be possible, and the clinical effects of different brands may not be comparable.

### *Standardization*

- Bilberry VMA (*V. myrtillus* anthocyanoside, the anthocyanoside component of the extract), standardized to contain 25% anthocyanidin, has been used in most European studies. However, the strength and dosing of preparations available in the United States may differ from those used in European studies. Patients may be advised to follow specific dosing instructions for each formulation.
- Mirtogenol®, a trademark of Indena S.p.A. and Horphag Research Ltd., is a patent pending proprietary combination of standardized bilberry extract Mirtoselect® and French maritime pine bark extract Pycnogenol®. Mirtoselect® is a standardized extract containing anthocyanins and is obtained exclusively from *V. myrtillus* L. fresh fruits that are harvested when ripe, between July and September. Mirtoselect® is a registered

trademark of Indena S.p.A., Milan, Italy. Pycnogenol®is a natural plant extract originating from the bark of the maritime pine that grows along the coast of southwest France and is found to contain a unique combination of procyanidins, bioflavonoids, and organic acids. Pycnogenol® is a registered trademark of Horphag Research Ltd., Guernsey.

### *Dosing*

**Adult (Age ≥ 18)**
**Oral.**

- *General*: Doses recommended by some healthcare providers based on traditional use are: fresh berries 55–115 g three times daily or 80–160 mg of aqueous extract three times daily (standardized to 25% anthocyanosides).
- *Acute diarrhea*: There is a lack of reliable clinical data to support the use of bilberry for diarrhea. Secondary sources recommend 4–8 g of dried fruit taken orally with water two times daily, decoction of dried fruit three times daily (made by boiling 5–10 g of crushed dried fruit in 150 mL of water for 10 min and straining while hot), or a cold macerate of dried fruit three times daily (made by soaking dried crushed fruit in 150 mL water for several hours). Some healthcare providers caution that for the treatment of diarrhea, only preparations of dried bilberry should be used, as the fresh fruit may actually have a laxative effect.
- *Circulatory and ophthalmologic uses*: Bilberry VMA extract doses range from 80 to 480 mg daily in 2–3 divided doses. However, 80 mg of the extract (standardized to contain 25% anthocyanidin) has been used twice daily (Jayle & Aubert, 1964; Jayle, Aubry, Gavini, Braccini, & De la Baume, 1965; Levy & Glovinsky, 1998; Mosci et al., 1988; Muth, Laurent, & Jasper, 2000; Perossini et al., 1987; Pautler, Maga, & Tengerdy, 1986; Spinella, 1985; Varma, Mizuno, & Kinoshita, 1977; Zadok et al., 1997; Zadok, Levy, & Glovinsky, 1999).
- *Dysmenorrhea*: 160 mg bilberry VMA extract, taken twice daily for 8 days, started 3 days prior to menses, has been used in a small trial (Colombo & Vescovini, 1985).
- *Ulcer prevention*: There is a lack of available human studies on ulcer prevention using bilberry. However, in rats, the natural flavonoid IdB1027 (VMA extract from bilberry) has demonstrated promising antiulcer effects (Lietti, Cristoni, & Picci, 1976; Magistretti et al., 1988; Mertz-Nielsen, Munck, Bukhave, & Rask-Madsen, 1990). Despite the

lack of human trials, some healthcare providers recommend half-a-cup of fresh bilberries (difficult to acquire in the United States) or 20–40 mg of standardized anthocyanidin extract three times daily (Colombo & Vescovini, 1985).

### *Topical.*

- *Mucus membrane inflammation*: Some healthcare providers recommend gargling a mouthwash of 10% dried fruit decoction as needed.

### *Children (Age < 18)*

- Insufficient available evidence.

### *Toxicology*

- Safety of bilberry fruit is often presumed based on bilberry's history as a food source. A literature review reveals neither animal nor human studies that report toxicity. In large quantities, acute toxicity may occur in the form of hydroquinone poisoning, anticoagulation, or gastrointestinal distress (Havsteen, 1983).

## *PRECAUTIONS/CONTRAINDICATIONS*

### *Allergy*

- Known allergy/hypersensitivity to bilberry, its constituents, or members of the Ericaceae family. A literature review reveals a lack of available reports of clinically significant allergic reactions.

### *Adverse Effects/Postmarket Surveillance*

- *General*: The long-term safety and side effects of bilberry have not been extensively studied. Safety is often presumed based on bilberry's history as a food source. Morazzoni and Bombardelli reported the results of French postmarketing surveillance data from 2,295 individuals who used the bilberry extract Tegens® before 1987 (Morazzoni & Magistretti, 1986). Adverse effects were experienced by 4% of patients overall, with

1% complaining of gastrointestinal discomfort and <1% experiencing nausea or heartburn.

- *Cardiovascular*: Bilberry has been theorized to potentially drop blood pressure, based on preclinical evidence of vascular smooth muscle-relaxing properties (Bettini, 1984; Bettini et al., 1984; Colantuoni, Bertuglia, Magistretti, & Donato, 1991). Bilberry products are sometimes marketed for the treatment of hypertension. However, a literature review reveals a lack of human data to support these assertions.
- *Endocrine*: Hypoglycemia has been demonstrated in animal studies, even in the setting of intravenous glucose administration (Allen, 1927; Bever, 1979; Cignarella et al., 1996). Human data are limited in this area. Based on a comparative study, bilberry extract may inhibit absorption of estrogens in the intestine by 75.5% ($p < .01$) (Fuchikami et al., 2006).
- *Gastrointestinal*: Theoretically, fresh bilberry fruit may have laxative effects. For this reason, only dried bilberry or preparations of dried bilberry are usually recommended for the treatment of diarrhea. However, large consumption of dried bilberries may cause constipation, according to a secondary source. One postmarket surveillance report of patients using bilberry extract (Tegens®) found that 1% of patients complained of gastrointestinal discomfort, and <1% experienced nausea or heartburn.
- *Hematologic*: With the use of bilberry leaf extract, there is a theoretical bleeding risk based on the antiplatelet and potential anticoagulant actions of bilberry extract, although there has been a lack of human reports of bleeding in the available literature (Bottecchia, 1987; Fdez et al., 1983; Morazzoni & Bombardelli, 1996; Pulliero et al., 1989; Zaragoza et al., 1985).

### *Precautions/Warnings/Contraindications*

- High quality long-term study on the side effects and safety of bilberry is currently lacking.
- Use cautiously in doses higher than recommended. European studies have used 25% anthocyanoside extract dosed at 80–160 mg, three times daily (Muth et al., 2000; Pulliero et al., 1989). Toxicity may theoretically occur at higher doses.
- Use bilberry cautiously in patients with bleeding disorders or in those using anticoagulant/antiplatelet medications, due to a theoretical increased risk of bleeding (Bottecchia, 1987; Fdez et al., 1983; Morazzoni & Bombardelli, 1996; Pulliero et al., 1989; Zaragoza et al., 1985).

- Use bilberry cautiously in patients with diabetes or in those taking hypoglycemic medications, due to theoretical risk of hypoglycemia (Allen, 1927; Bever, 1979; Cignarella et al., 1996).
- Safety during pregnancy and lactation has not been clearly established. However, bilberry is presumed by many to be safe, based on the use of bilberry as a food product.
- Avoid ingesting bilberry leaves; some healthcare providers suggest possible toxicity.

### *Pregnancy and Lactation*

- Safety of bilberry during pregnancy or lactation has not been established or studied systematically. However, one study used bilberry extract to treat pregnancy-induced lower extremity edema, and no adverse effects were reported (Grismondi, 1981). Bilberry fruit is presumed to be safe on the basis of the use of bilberry as a food product in nonallergic individuals.

## *INTERACTIONS*

### *Bilberry/Drug Interactions*

- *Antibiotics*: Based on an in vitro study, bilberry leaves may have antibacterial properties (Brantner & Grein, 1994).
- *Anticoagulants and antiplatelets*: There is a theoretical bleeding risk based on the antiplatelet and potential anticoagulant actions of bilberry extract, although there has been a lack of human reports of bleeding in the available literature (Bottecchia, 1987; Fdez et al., 1983; Morazzoni & Bombardelli, 1996; Pulliero et al., 1989; Zaragoza et al., 1985).
- *Antidiabetic agents*: In animal studies, bilberry leaf extract lowered glycemic levels in diabetic rats, normal dogs, and depancreatized dogs (Allen, 1927; Bever, 1979; Cignarella et al., 1996). However, another study using healthy rats found that an alcoholic extract of *V. myrtillus* leaves increased serum glucose levels compared to controls (Neef, Declercq, & Laekeman, 1995).
- *Antidiarrheals*: Bilberry contains tannins that have been used medicinally as astringents and to treat diarrhea.
- *Antihypertensives*: Bilberry has been theorized to potentially drop blood pressure, based on preclinical evidence of vascular smooth muscle-relaxing properties (Bettini, 1984; Bettini et al., 1984; Colantuoni

et al., 1991). Anthocyanoside extracts have been shown to have smooth muscle-relaxing activity, which may account for its purported effects in one series of women with dysmenorrhea (Colombo & Vescovini, 1985). Bioflavonoids and extracts of anthocyanosides (such as those present in bilberry) have been shown to relax vascular smooth muscles in experimental models, possibly via stimulation of prostaglandins (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991).

- *Antineoplastic agents:* Based on an in vitro study, bilberry (*V. myrtillus* L.) may inhibit cancer cell growth (Zhao et al., 2004).
- *Antioxidants*: Bilberry contains anthocyanosides that are flavonoid derivatives of anthocyanins (the blue, red, or violet pigments found in many berry varieties), which are closely related in structure and activity to flavonoids (Havsteen, 1983) and possess free radical scavenging/antioxidant properties. Antioxidant properties have been attributed to bilberry based on in vitro studies (Laplaud et al., 1997; Martin-Aragon et al., 1998, 1999; Prior et al., 1998), although studies in humans are not available.
- *Antiulcer agents*: Based on an animal study, large doses of cyaniding chloride from bilberry may have antiulcer activity (Cristoni & Magistretti, 1987; Magistretti et al., 1988; Mertz-Nielsen et al., 1990).
- *Estrogens*: Based on a comparative study, bilberry extract may inhibit absorption of estrogens in the intestine by 75.5% ($p < .01$) (Fuchikami et al., 2006).
- *Hepatotoxic agents*: Based on animal research, anthocyans may have a protective effect on liver cells (Mitcheva, Astroug, Drenska, Popov, & Kassarova, 1993).

### *Bilberry/Herb Interactions*

- *Antibacterials*: Based on an in vitro study, bilberry leaves may have antibacterial properties (Brantner & Grein, 1994).
- *Anticoagulants and antiplatelets*: There is a theoretical bleeding risk based on the antiplatelet and potential anticoagulant actions of bilberry extract, although there has been a lack of human reports of bleeding in the available literature (Bottecchia, 1987; Fdez et al., 1983; Morazzoni & Bombardelli, 1996; Pulliero et al., 1989; Zaragoza et al., 1985).
- *Antidiarrheals*: Bilberry contains tannins that have been used medicinally as astringents and to treat diarrhea.
- *Antineoplastics*: Based on an in vitro study, bilberry (*V. myrtillus* L.) may inhibit cancer cell growth (Zhao et al., 2004).

- *Antioxidants*: Bilberry contains anthocyanosides that are flavonoid derivatives of anthocyanins (the blue, red, or violet pigments found in many berry varieties), which are closely related in structure and activity to flavonoids (Havsteen, 1983) and possess free radical scavenging/antioxidant properties. Antioxidant properties have been attributed to bilberry based on in vitro studies (Laplaud et al., 1997; Martin-Aragon et al., 1998, 1999; Prior et al., 1998), although studies in humans are not available.
- *Antiulcer agents*: Based on an animal study, large doses of cyaniding chloride from bilberry may have antiulcer activity (Cristoni & Magistretti, 1987; Magistretti et al., 1988; Mertz-Nielsen et al., 1990).
- *Hepatotoxic herbs*: Based on animal research, anthocyans may have a protective effect on liver cells (Mitcheva et al., 1993).
- *Hypoglycemics*: In animal studies, bilberry leaf extract lowered glycemic levels in diabetic rats, normal dogs, and depancreatized dogs (Allen, 1927; Bever, 1979; Cignarella et al., 1996). However, another study using healthy rats found that an alcoholic extract of *V. myrtillus* leaves increased serum glucose levels compared to controls (Neef et al., 1995).
- *Hypotensives*: Bilberry has been theorized to potentially drop blood pressure, based on preclinical evidence of vascular smooth muscle-relaxing properties (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991). Anthocyanoside extracts have been shown to have smooth muscle-relaxing activity, which may account for its purported effects in one series of women with dysmenorrhea (Colombo & Vescovini, 1985). Bioflavonoids and extracts of anthocyanosides (such as those present in bilberry) have been shown to relax vascular smooth muscles in experimental models, possibly via stimulation of prostaglandins (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991).
- *Phytoestrogens*: Based on a comparative study, bilberry extract may inhibit absorption of estrogens in the intestine by 75.5% ($p < .01$) (Fuchikami et al., 2006).
- *Quercetin*: Bilberry may be a source of bioavailable quercetin, therefore, additive effects may be seen with concomitant administration (Erlund et al., 2003).
- *Resveratrol*: Based on laboratory studies, bilberry may contain resveratrol (Lyons et al., 2003; Rimando, Kalt, Magee, Dewey, & Ballington, 2004); therefore, additive effects may be seen with concomitant administration.

- *Vitamin C*: Based on a clinical study of subjects with normal platelet aggregation, ingestion of *V. myrtillus* anthocyanins and ascorbic acid may additively reduce platelet aggregation (Pulliero et al., 1989).

### *Bilberry/Food Interactions*

- Insufficient available evidence.

### *Bilberry/Lab Interactions*

- *Blood pressure*: Bilberry has been theorized to potentially drop blood pressure, based on preclinical evidence of vascular smooth muscle-relaxing properties (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991). Anthocyanoside extracts have been shown to have smooth muscle-relaxing activity, which may account for its purported effects in one series of women with dysmenorrhea (Colombo & Vescovini, 1985). Bioflavonoids and extracts of anthocyanosides (such as those present in bilberry) have been shown to relax vascular smooth muscles in experimental models, possibly via stimulation of prostaglandins (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991).
- *Coagulation panel*: Bilberry extract has been shown to have potential anticoagulant and antiplatelet actions, although there has been a lack of human reports of bleeding in the available literature (Bottecchia, 1987; Fdez et al., 1983; Morazzoni & Bombardelli, 1996; Pulliero et al., 1989; Zaragoza et al., 1985).
- *Serum glucose*: Hypoglycemia has been demonstrated in animal studies. Rats given an extract made from bilberry developed hypoglycemia, even in the setting of intravenous glucose administration (Allen, 1927; Bever, 1979; Cignarella et al., 1996). Human data are lacking.

## *MECHANISM OF ACTION*

### *Pharmacology*

- *Constituents*: Bilberry contains several compounds that have demonstrated biological activity. The main chemicals contained in bilberry extract have been shown to be: anthocyanins (Milbury, Graf, Curran-Celentano, & Blumberg, 2007; Wu, Koponen, Mykkanen, & Torronen, 2007), flavonoids, hydroquinone, oleanolic acid, neomyrtillin, sodium,

tannins, and ursolic acid (Havsteen, 1983; Lietti et al., 1976; Lietti & Forni, 1976; Marcollet, Bastide, & Tronche, 1970; Mian, 1977). Bilberry also contains resveratrol (Lyons et al., 2003; Rimando et al., 2004). The anthocyanosides, tannins, and flavonoids have been of particular scientific interest. Flavonoids have been shown in vitro to possess a number of biological properties, including inhibition of prostacyclin synthesis, reduction of capillary permeability and fragility, free radical scavenging, inhibition of a wide range of enzymes, impairment of coagulation and platelet aggregation, and anticarcinogenicity (Mian, 1977; Bomser et al., 1996).

- *Mechanism of action*: Anthocyanins and other phenolics from bilberry upregulate the oxidative stress defense enzymes heme-oxygenase-1 and glutathione S-transferase-pin cultured human retinal pigment epithelial cells, suggesting that they stimulate signal transduction pathways, influencing genes controlled by the antioxidant response element (Milbury et al., 2007).
- *Antibacterial effects*: In an in vitro study using *Staphylococcus aureus*, *S. aureus* Oxford, *Enterococcus faecalis*, *Bacillus subtilis*, and *Escherichia coli*, an aqueous extract of bilberry leaves had a MIC of 12.7–17.8 mg/mL and an aqueous extract of bilberry fruit had a MIC of 15.4–30.7 mg/mL (Brantner & Grein, 1994).
- *Anticarcinogenic effects*: In an in vitro study, anthocyanin-rich extracts from bilberry (*V. myrtillus* L.) inhibited the growth of a colon cancer cell line (Zhao et al., 2004).
- Bomser et al. (1996) screened fruit extracts of bilberry for potential anticarcinogenic compounds by a combination of fractionation and in vitro testing of their ability to induce the Phase 2 xenobiotic detoxification enzyme quinone reductase (QR) and to inhibit the induction of ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine synthesis, by the tumor promoter phorbol 12-myristate 13-acetate (TPA). The crude extracts, anthocyanin, and proanthocyanidin fractions were not found to be highly active in Phase 2 xenobiotic detoxification enzyme QR induction, whereas the ethyl acetate extracts were active QR inducers. The concentrations required to double QR activity (designated CDqr) for the ethyl acetate extracts of bilberry were 1.0 mcg tannic acid equivalents (TAE). Further fractionation of the bilberry ethyl acetate extract revealed that the majority of inducer potency was contained in a hexane/chloroform subfraction (CDqr = 0.07 mcg TAE). The anthocyanidin and ethyl acetate extracts of bilberry were either inactive or relatively weak inhibitors of ODC activity. The authors concluded that components of the hexane/chloroform fraction of bilberry exhibit

potential anticarcinogenic activity, as evaluated by in vitro screening tests.

- *Antihyperglycemic effects*: In normal and depancreatized dogs, oral administration of bilberry leaves reduced hyperglycemia, even when the glucose was injected intravenously concurrently (Allen, 1927; Bever, 1979).
- *Antioxidant effects*: Bilberry contains anthocyanosides that are flavonoid derivatives of anthocyanins (the blue, red, or violet pigments found in many berry varieties), which are closely related in structure and activity to flavonoids (Havsteen, 1983) and possess free radical scavenging/antioxidant properties. Antioxidant properties have been attributed to bilberry based on in vitro studies (Laplaud et al., 1997; Martin-Aragon et al., 1998, 1999; Prior et al., 1998).
- *Antiplatelet activity*: In a clinical study of 30 subjects with normal platelet aggregation, 480 mg of Myrtocyan® (*V. myrtillus* anthocyanins) daily, 3 g of ascorbic acid daily, or both treatments all reduced platelet aggregation after 30 and 60 days (Pulliero et al., 1989). Bilberry anthocyanins reduced platelet aggregation more than ascorbic acid alone, but bilberry anthocyanins and ascorbic acid together were the most effective. Also, in in vitro studies, anthocyanins extracted from bilberry have inhibited platelet aggregation (Bottecchia, 1987; Fdez et al., 1983; Morazzoni & Bombardelli, 1996; Zaragoza et al., 1985).
- Flavonoids have been shown in vitro to inhibit prostacyclin synthesis. In one animal model, *V. myrtillus* anthocyanosides were studied for their effects on prostacyclin-like activity in rat arterial issue (Morazzoni & Magistretti, 1986).
- *Antiproliferative effects*: According to one laboratory study, anthocyanins were the predominant phenolic compounds in bilberry extracts (Wu et al., 2007). Compared to other plants with anthocyanins, such as black currant or lingonberry, cell growth inhibition was greater for bilberry than other plants studied. The proapoptosis marker, Bax, was increased 1.3-fold in bilberry-treated cells, whereas the prosurvival marker, Bcl-2, was detected only in control cells. The results demonstrated that bilberry and other berry extracts containing anthocyanins inhibited cancer cell proliferation, mainly via the p21WAF1 pathway.
- *Antiulcer effects*: In an animal study, large doses of cyanidin chloride from bilberry significantly increased gastric mucosal release of prostaglandin E2 (Mertz-Nielsen et al., 1990). In animal models of gastric ulcers, cyanidin chloride showed antiulcer activity (Cristoni & Magistretti, 1987; Magistretti et al., 1988).

- *Astringent effects*: Bilberry contains tannins that have been used medicinally as astringents and to treat diarrhea.
- *Connective tissue stabilizing effects*: An in vitro study has suggested that anthocyanosides appear to stabilize connective tissue by enhancing collagen synthesis, inhibiting collagen degradation, and enhancing collagen cross linking (Jonadet, Meunier, Bastide, & Bastide, 1983). In contrast, Boniface and Robert (1996) found a significant decrease in connective tissue synthesis (collagen and glycoproteins) in gingival tissue samples of 12 adult diabetics treated with 600 mg of anthocyanosides daily for 2 months.
- *Hepatoprotective activity*: In an animal study, anthocyans exerted a protective effect on liver cells (Mitcheva et al., 1993).
- *Hyperglycemic effects*: In an oral glucose tolerance test in healthy rats, an alcoholic extract of *V. myrtillus* leaves increased serum glucose levels compared to controls (Neef et al., 1995).
- *Hypotensive effects*: Bilberry has been theorized to potentially drop blood pressure, based on preclinical evidence of vascular smooth muscle-relaxing properties (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991).
- Anthocyanoside extracts have been shown to have smooth muscle-relaxing activity, which may account for their purported effects in one series of women with dysmenorrhea (Colombo & Vescovini, 1985). Bioflavonoids and extracts of anthocyanosides (such as those present in bilberry) have been shown to relax vascular smooth muscles in experimental models, possibly via stimulation of prostaglandins (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991).
- *Intracellular signaling effects*: Anthocyanosides have been shown to inhibit cAMP phosphodiesterase, which is involved in intracellular signal transduction pathways (Magistretti et al., 1988).
- *Ocular effects*: Anthocyanosides have been shown to exert direct effects on the retina, including the alteration of local enzymatic reactions and enhancement of the recovery of rhodopsin (Cluzel et al., 1970). The multiingredient product Mirtogenol™ (Pycnogenol®—French maritime pine bark extract and Mirtoselect®—standardized bilberry extract) has been reported to lower intraocular pressure (IOP) and improve ocular blood flow (Steigerwalt et al., 2008).
- *Smooth muscle relaxant effects*: Anthocyanoside extracts have been shown to have smooth muscle-relaxing activity, which may account for their purported effects in one series of women with dysmenorrhea (Colombo & Vescovini, 1985). Bioflavonoids and extracts of

anthocyanosides (such as those present in bilberry) have been shown to relax vascular smooth muscles in experimental models, possibly via stimulation of prostaglandins (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991).
- *Vasoprotective effects*: Flavonoids have been shown in vitro to reduce capillary permeability and fragility. Anthocyanosides have been studied for their potential protective effect in disorders due to abnormal capillary fragility (Mian, 1977).

### *Pharmacodynamics/Kinetics*

- There are limited data regarding the pharmacodynamics and kinetics of *V. myrtillus* (bilberry) anthocyanosides (VMA). In one animal study, bilberry anthocyanosides were rapidly distributed after intraperitoneal injection and intravenous administration (Morazzoni, Livio, Scilingo, & Malandrino, 1991). In another animal study, bilberry anthocyanosides were found to be eliminated via the bile and urine with a modest level of liver extraction (Lietti & Forni, 1976).
- Bioavailability in animals is low. Following oral doses in rats, plasma levels of VMA reached a peak at 15 min and declined rapidly within 2 hr, and the absolute bioavailability was 1.2% of the administered dose (Morazzoni et al., 1991). The gastrointestinal absorption of VMA was 5% of the administered dose. Another study found a differential affinity of VMA for certain tissues (especially skin and kidney) (Lietti et al., 1976). This suggests that different tissues may have more persistent local concentrations.

## *HISTORY*

- The bilberry plant is a deciduous, leafy, freely branched, perennial shrub that is native to northern Europe, northern United States, and Canada. It is found in heaths, moors, and woods in most of Europe, northern Asia, and in the mountain/subalpine of western North America. Bilberry grows to 35–60 cm in height and flowers from April through June. It produces a fruit similar to the American blueberry, and the ripe fruits can be collected from July through September. The name bilberry is derived from the Danish word, *bollebar*, which means "dark berry." The berries are purple-black in color and coarsely wrinkled. The berries contain many small, shiny, brownish-red seeds.

- Bilberry's medicinal use was described by the 12th Century German herbalist Hildegard von Bingen (1098–1179), who purportedly recommended it for the induction of menses. Herbalists in the 1700s reported its use as well. Decoctions of the dried fruit have a long history of oral use to treat diarrhea and of topical use to treat mild inflammation of the mouth and mucus membranes. Bilberry preparations have also been used traditionally to help stop the flow of breast milk and as a treatment for urinary complaints, including nephrolithiasis and urinary tract infections. Tea made from bilberry plant leaves has a long history of use in the management of diabetes mellitus. Bilberry has also traditionally been used as a nutritional supplement in the treatment or prevention of scurvy due to its vitamin C content.
- The modern use of bilberry in the treatment of various visual disorders dates to World War II. British Royal Air Force pilots reported that the ingestion of bilberry jam just prior to missions seemed to improve their vision. Poor-quality studies during the 1960s and 1970s purportedly supported these claims. Recently, there have been several open trials and some randomized trials in the European literature investigating the use of bilberry in treating and preventing various visual disorders. Today, bilberry and VMA extracts are used as prophylaxis against cataracts, diabetic retinopathy, glaucoma, macular degeneration, and impaired night vision. Some European surgeons also use VMA extract to promote surgical wound healing.
- Bilberry is also commonly used to make jams, pies, cobblers, syrups, and alcoholic/nonalcoholic beverages, and fruit extracts are used as a coloring agent in wines.

**Condition:** Refers to the medical condition or disease targeted by a therapy.

Study Design: Common types include:

- **RCT**: An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.

# EVIDENCE TABLE

| Condition | Study Design | Author (Year) | *N* | Statistically Significant? | Quality of Study 0–2 = poor 3–4 = good 5 = excellent | Magnitude of Benefit | (ARR) | (NNT) | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Cataracts | Double-blind placebo-controlled | Bravetti, Fraboni, and Maccolini (1989) | 50 | Unclear | NA | Large | NA | NA | Combined treatment with vitamin E. |
| CVI | Single-blind placebo-controlled | Gatta (1988) | 60 | Yes | 2 | Small | NA | NA | 30-day trial showing significant improvement, but poor methodological quality. |
| Dysmenorrhea | Randomized double-blind | Colombo and Vescovini (1985) | 30 | Yes | 2 | NA | NA | NA | Treatments 3 days prior to and during menses reduced nausea, vomiting, and headache in treatment group versus placebo. |
| Fibrocystic breast disease | Case series | Leonardi (1993) | 257 | NA | NA | Medium | NA | NA | Open trial measuring improvements from baseline. |
| Glaucoma (intraocular eye pressure) | Controlled trial, nonblinded | Steigerwalt et al. (2008) | 38 | Yes | 1 | Small | NA | NA | Used a multiingredient product called Mirtogenol™ once in the morning and once in the evening for 6 months. No placebo group. |
| Retinopathy (diabetic, vascular) | Double-blind placebo-controlled | Perossini et al. (1987) | 40 | Yes | 2 | NA | NA | NA | Ophthalmoscopic improvement in 77–90% of treated patients. Poor description of methodology. |
| Retinopathy (diabetic, vascular) | Controlled trial | Repossi, Malagola, and De Cadilhac (1987) | NA | Yes | 1 | NA | NA | NA | Opthalmoscopic endpoints. |
| Retinopathy (diabetic, vascular) | Case series | Mosci et al. (1988) | 30 | Yes | NA | Medium | NA | NA | Subjects with and without retinopathy given procyanidolic anthocyanosides. Positive opthalmoscopic endpoints, but statistical significance was not calculated. |

*(Continued on next page)*

## EVIDENCE TABLE *(Continued)*

| Condition | Study Design | Author (Year) | *N* | Statistically Significant? | Quality of Study 0–2 = poor 3–4 = good 5 = excellent | Magnitude of Benefit | (ARR) | (NNT) | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Retinopathy (diabetic, vascular) | Case series | Scharrer and Ober (1981) | 31 | No | NA | Small | NA | NA | Small study; included small numbers of other eye disorders (macular degeneration, anticoagulant-related hemorrhage). |
| Retinopathy (diabetic, vascular) | Case series | Lagrue et al. (1979) | 54 | Unclear | NA | Small | NA | NA | Examined polymeric collagen and structural glycoprotein levels. |
| Night vision | Systematic review | Canter and Ernst (2004) | 12 | No | NA | NA | NA | NA | Of the 12 studies included, four randomized controlled trials found no significant effect, and one RCT and seven lesser quality studies found a positive effect. |
| Night vision | Double-blind placebo-controlled crossover | Muth et al. (2000) | 15 | No | 3 | None | NA | NA | Three weeks of high-dose VMA failed to show an effect on night vision. |
| Night vision | Double-blind placebo-controlled crossover | Levy and Glovinsky (1998) | 16 | No | 3 | None | NA | NA | Negative study, but no power calculations were done. Examined single-dose VMA effect on three tests of night vision. |
| Night vision | Double-blind placebo-controlled crossover | Zadok et al. (1997, 1999) | 18 | No | 3 | None | NA | NA | Early negative study with ophthalmoscopic endpoints. Power calculation performed, but small study. |
| Night vision | Placebo-controlled | Jayle et al. (1965) | 60 | Yes | 3 | Medium | NA | NA | Limited description of blinding, randomization, and measurement technique. |
| Night vision | Placebo-controlled | Jayle and Aubert (1964) | 40 | Yes | 2 | Small | NA | NA | Crossover design. Limited description of blinding, randomization, and measurement technique. |

- **Equivalence trial**: An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- **Before and after comparison**: A study that reports only the change in outcome in each group of a study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- **Case series**: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterward). Case series are considered weak evidence of efficacy.
- **Case-control study**: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary and alternative medicine literature.
- **Cohort study**: A study which assembles a group of patients with certain baseline characteristics (e.g., use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary and alternative medicine literature.
- **Meta-analysis**: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.
- **Review**: An author's description of his or her opinion based on personal, nonsystematic review of the evidence.
- **Systematic review**: A review conducted according to prespecified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.
- **P**: Pending verification.

**Author (Year)**: Identifies the study being described in a row of the table.
$N$: The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as $N$. $N$ includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. (For systematic reviews

the number of studies included is reported. For metaanalyses, the number of total subjects included in the analysis or the number of studies may be reported.) P = pending verification.

**Statistically Significant?**: Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *p* values). P = pending verification.

**Quality of Study**: A numerical score between 0 and 5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (1996). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" section of reviews).

- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point toward an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0–5.

Jadad Score Calculation

| Item | Score |
|---|---|
| Was the study described as randomized (this includes words such as randomly, random, and randomization)? | 0/1 |
| Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)? | 0/1 |
| Was the study described as double-blind? | 0/1 |
| Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.)? | 0/1 |
| Was there a description of withdrawals and dropouts? | 0/1 |
| Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.). | 0/−1 |
| Deduct one point if the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy). | 0/−1 |

### *Magnitude of Benefit*

This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant, "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:

- Large: if $>$ 1 SD
- Medium: if 0.5 to 0.9 SD
- Small: if 0.2 to 0.4 SD

### *P = Pending Verification*

In many cases, studies do not report the SD of change of the outcome measure. However, the change in the SD of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled SD (Effect size = [mean treatment − mean placebo]/$SD_p$).

### *Absolute Risk Reduction (ARR)*

This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, ARR equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ([control event rate − experimental event rate]/control event rate). Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column. P = pending verification.

### *Number Needed to Treat (NNT)*

This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one

person to experience the specified benefit. It is calculated by dividing the ARR into 1 (1/ARR). P = pending verification.

### *Comments*

When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc.). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

## *EVIDENCE DISCUSSION*

### *Atherosclerosis and Peripheral Vascular Disease*

- *Summary*: Bilberry has been used traditionally to treat symptoms of vascular disease, including coronary artery disease. However, there is limited human research in this area currently available. Preliminary evidence from numerous in vitro and animal studies has suggested that bilberry extracts may be useful in the prevention of vascular disease (Colantuoni et al., 1991; Detre, Jellinek, Miskulin, & Robert, 1986; Gabor, 1972) and may reduce oxidation of low density lipoproteins (LDL) (Cignarella et al., 1996; Laplaud et al., 1997; Rasetti et al., 1997; Viana et al., 1996). Without additional human data, a recommendation cannot be made either in favor or against this use of bilberry.
- *Preclinical evidence*: Bilberry extracts have been shown to decrease platelet aggregation and LDL oxidation in animal models (Buliero, 1989; Laplaud et al., 1997). In an animal experiment looking at ischemia-reperfusion injury in hamster cheek microcirculation, *V. myrtillus* (bilberry) anthocyanoside (VMA) extract was shown to reduce microvascular impairment after reperfusion (Bertuglia, Malandrino, & Colantuoni, 1995). In another animal study, VMA extract was shown to reduce vascular permeability in the setting of hypertension (Detre et al., 1986). Decreases in lipid deposition and intimal proliferation have also been demonstrated in VMA-treated animals (Kadar et al., 1979). These studies suggest that there may be a vasoprotective role for VMA in the prevention of vascular disease.

### *Cataracts*

- *Summary*: Bilberry extract has been used and recommended clinically for a number of eye disorders, including the prevention of cataract progression. It has been hypothesized that the bioflavonoids in bilberry may benefit patients with cataracts. At this time, there are limited data available in support of this use of bilberry or quercetin (also a source of bioflavonoids) (Varma et al., 1977).
- *Evidence*: In one case series of 50 elderly Italians with early stage cataracts (62 eyes studied), a combination of vitamin E and anthocyanosides (extracted from bilberry) was found to slow the progression of lens opacities in 97% of cases (Bravetti et al., 1989). However, without controls, the progression rate in the absence of bilberry cannot be assessed. In addition, the effects of bilberry cannot be separated from vitamin E.

### *Chronic Venous Insufficiency (CVI)*

- *Summary*: CVI is a syndrome that is characterized by lower extremity edema, varicosities, pain, pruritus, atrophic skin changes, and ulcerations. *Vaccinium myrtillus* anthocyanoside (VMA), an extract of bilberry standardized to 25% anthocyanin, is often used in Europe for the treatment of CVI. A literature review reveals that several human case series and a single-blind trial have reported significant improvements in edema and lower extremity discomfort related to CVI. However, due to methodological weaknesses with the available data, there is not sufficient evidence to recommend either for or against the use of bilberry extract for CVI.
- *Evidence*: Bilberry extract has been shown to exert potent effects on vascular permeability and fragility in animal and in vitro models. VMA extracts have been widely used in Europe for arterial, venous, and capillary disorders.
- A single-blind placebo-controlled study in 60 patients with CVI showed a significant reduction in symptom severity after 30 days of bilberry therapy (Gatta, 1988). Subjects were given bilberry extract equivalent to 173 mg of anthocyanins daily or placebo. Reporting of blinding technique and randomization was limited, thus weakening the conclusions of this trial.
- *Studies of lesser design strength*: A number of case series of poor methodological quality conducted between 1968 and 1985 reported

positive findings. These results can only be considered preliminary, due to a lack of statistical analysis in some cases, inconsistent classification of subjects, and the use of nonvalidated measurement instruments to measure outcomes. Since the signs and symptoms of CVI may fluctuate over time, the lack of controls makes it impossible to discern if improvements were due to bilberry or to the natural history of the disease. Coget and Merlen (1968) administered 100–150 mg of bilberry anthocyanins daily for 2 weeks per month over 2 months to 27 subjects with varicosities or other lower extremity venous malformations. Subjective improvements in edema, pain, and bruising were reported with no statistical analysis provided. In a French case series, a heterogeneous group of patients with "lowered capillary resistance" was treated with VMA extract (Difrarel® 100 mg of anthocyanins, four tablets daily) for 12–69 days (mean 28 days) (Amouretti, 1972). The authors reported a mean increase in capillary resistance over baseline. However, the study enrolled 40 patients with diverse conditions, including atherosclerosis, hypertension, and venous insufficiency of the lower limbs, thus limiting generalization. Ghiringhelli, Gregoratti, and Marastoni (1978) studied 480 mg of bilberry anthocyanins daily (Tegens®) for 1 month in 47 subjects with CVI. Statistically significant improvements in lower extremity edema and subjective pain and burning were reported. However, it was not reported if concomitant therapies were used during the trial period. In a 6-month study, Tori and D'Errico (1980) administered 480 mg of bilberry anthocyanins daily (Tegens®) to 97 patients with lower extremity varicosities. Statistically significant improvements were reported in measurements of edema and discomfort, although it is not clear that the measurements used would be reproducible. Based on these studies, no definitive conclusions can be drawn regarding the use of bilberry in CVI.

### *Diabetes Mellitus*

- *Summary*: Bilberry is a traditional therapy used to treat diabetes. Tea made from the leaves of bilberry is often used for this indication. Limited animal data suggest that bilberry leaf extract possesses hypoglycemic and lipid-lowering properties that may be beneficial in patients with diabetes (Cignarella et al., 1996). However, because there is a lack of available human trials evaluating the safety or efficacy of the use of bilberry leaf extract as a hypoglycemic agent or interactions of bilberry

leaf extract with oral hypoglycemic medications, bilberry cannot be recommended for the treatment of diabetic patients.

### *Diarrhea*

- *Summary*: Treatment of diarrhea is a popular use of bilberry products. However, a literature review reveals no laboratory, animal, or human studies investigating this role for bilberry products. Therefore, this indication cannot be based on scientific merit.

### *Dysmenorrhea*

- *Summary*: Limited evidence suggests that bilberry extract may improve symptoms associated with dysmenorrhea, such as headache, nausea, vomiting, and pelvic pain. However, at this time, the data are not sufficient to recommend either for or against this use of bilberry.
- *Evidence*: Bioflavonoids and extracts of anthocyanosides (such as those present in bilberry) have been shown to relax vascular smooth muscles in experimental models, possibly via stimulation of prostaglandins (Bettini, 1984; Bettini et al., 1984; Colantuoni et al., 1991). It has been hypothesized that such smooth muscle-relaxing effects might improve the symptoms of dysmenorrhea.
- Colombo and Vescovini (1985) performed a small ($n = 30$), placebo-controlled, double-blind study that examined the treatment of dysmenorrhea. A dose of 160 mg twice daily of bilberry *V. myrtillus* anthocyanoside (Tegens®) was started 3 days prior to menses and continued for 8 days and repeated for two consecutive menstrual cycles. This treatment was found to statistically significantly reduce pelvic pain, lumbosacral pain, breast pain, nausea, vomiting, and headache vs. placebo. However, there was limited description of blinding, randomization, measurement instruments used, patient baseline characteristics, and statistical analysis. Therefore, this trial can only be considered suggestive and not definitive.

### *Fibrocystic Breast Disease*

- *Summary*: There is preliminary evidence suggesting a possible benefit of bilberry in the treatment of fibrocystic disease of the breast.

- *Evidence*: A case series examining bilberry extract in the treatment of fibrocystic mastopathy reported encouraging early results. Marked improvement was seen in 33% of patients, reduction in symptoms was reported in 27%, and complete resolution was reported in 6% of patients. However, no effect was seen in 32% of patients (Leonardi, 1993). Without a control group, it is not clear to what extent improvements would have occurred spontaneously. Therefore, results can only be considered preliminary.

### *Glaucoma*

- *Summary*: High IOP is considered a risk factor for developing glaucoma. In a 2008 study, patients using Mirtogenol™, a multiingredient product of standardized bilberry and Pycnogenol®, showed significant reductions in intraocular eye pressure after 3 months. However, available human evidence is methodologically flawed and additional studies are needed to confirm these initial findings.
- *Evidence*: Steigerwalt et al. (2008) conducted a study to assess the ability of Mirtogenol™ to lower high IOP. Of 38 subjects, 20 were given Mirtogenol™ once in the morning and once in the evening for 6 months, and 16 were controls who received no treatment. Each Mirtogenol™ tablet contained 40 mg of Pycnogenol®, French maritime pine bark extract and 80 mg of Mirtoselect®, standardized bilberry extract. The IOP was measured with the standard Goldmann applanation tonometer at the same time in the morning. Prior to testing, subjects had complete eye exams, ocular hypertension and no signs of glaucoma. After 3 months of treatment with Mirtogenol™, the IOP was significantly lowered compared to that of untreated controls ($p < .05$). No further improvement was found after 6 months. No side effects were observed. Ocular blood flow (central retinal, ophthalmic, and posterior ciliary arteries) also improved both in the systolic and diastolic components as measured by Color Doppler imaging ($p < .05$). The authors suggested that Mirtogenol™might lower the risk for developing symptomatic glaucoma by controlling IOP and improving ocular blood flow. However, limitations of this study included a lack of placebo group, double-blinding and randomization. The use of a multiingredient product also makes it difficult to discern the effects of bilberry alone.

### *Peptic Ulcer Disease (PUD)*

- *Summary*: Bilberry extract has been suggested as a promoter of gastric ulcer healing, with support from animal data (Cristoni & Magistretti, 1987). In rats, a natural flavonoid IdB1027 (VMA extract from bilberry) has demonstrated promising antiulcer effects (Lietti et al., 1976; Lietti & Forni, 1976; Magistretti et al., 1988; Mertz-Nielsen et al., 1990). Berry extracts have been shown to inhibit *Helicobacter pylori* bacteria in vitro and to enhance susceptibility to clarithromycin (Chatterjee, Yasmin, Bagchi, & Stohs, 2004). At this time, however, there is not enough adequate human evidence to recommend for or against this use of bilberry. It should be noted that the bacteria *H.pylori* has been implicated in many cases of gastric and duodenal ulcers, and testing and/or treatment for *H. pylori* should be considered in patients with known or suspected PUD.

### *Retinopathy (Diabetic, Vascular)*

- *Summary*: Although the efficacy of bilberry in the treatment of retinal and microvascular disease of diabetes has yet to be firmly established, many animal studies and a few small placebo-controlled trials have reported promising results in this area. Clinical trials in the European literature, mostly from Italy, have reported effects on parameters of retinopathy and microangiopathy in humans.
- *Preclinical evidence*: Numerous animal experiments have documented protective effects of *V. myrtillus* anthocyanoside (VMA), an extract of bilberry standardized to 25% anthocyanin, on blood vessels (Colantuoni et al., 1991; Gabor, 1972; Lietti et al., 1976; Lietti & Forni, 1976). VMA has been shown to improve microvascular oxygen delivery and to function as an antioxidant and antiinflammatory agent. Lagrue et al. (1979) demonstrated improvements in levels of "pathologic proteins" (collagen and structural lipoprotein levels) in diabetic microangiopathy. These early data have made bilberry an attractive candidate for use in patients with diabetic retinopathy and microangiopathy; both involve vascular damage at the level of the small blood vessel.
- *Evidence*: A double-blind, placebo-controlled study was conducted in 40 patients with vascular retinopathy (diabetic or hypertensive) (Perossini et al., 1987). Bilberry extract (Tegens®) was administered at a dose of 160 mg twice daily for 1 month. Placebo patients were then given bilberry for 1 month (although bilberry patients were not crossed over

to placebo). Moderate mean improvements in ophthalmoscopic and fluoroangiographic findings were found following bilberry treatment, as measured by a multiitem clinician questionnaire. According to the authors, a 77–90% improvement was seen in bilberry-treated patients. The clinical validity of these results is limited by the lack of adequate description of blinding or randomization and by the lack of crossover of the placebo group (preventing true between-group comparisons).

- In a case series, Mosci et al. (1988) dosed 30 subjects (10 with diabetic retinopathy, 10 with nondiabetic retinopathy, and 10 normal "controls") with procyanidolic anthocyanosides. A statistically significant improvement in microangiopathic measures was noted for patients with retinopathy, although details of measurement instrument and method of analysis were not reported.
- Similar effects have been demonstrated in additional small studies of poor methodological quality by Repossi, Malagola, and De Cadilhac (1987) and Scharrer and Ober (1981).

### *Night Vision*

- *Summary*: Uncontrolled studies during the 1960s and 1970s and anecdotal reports suggested a beneficial effect of bilberry on night vision. However, more recent controlled human trials with well-defined outcomes have failed to demonstrate any effect. Although these trials have been methodologically flawed, the balance of available evidence suggests a lack of efficacy. It is possible that the doses used have not been adequate to elicit a measurable effect. Nonetheless, without additional positive evidence from well-designed trials, the use of bilberry products for night vision cannot be considered scientifically supported.
- *Evidence*: Canter and Ernst (2004) conducted a systematic review by searching Medline, EMBASE, AMED, CINAHL, PsycINFO, and CCTR (Cochrane) databases from the inception of the databases to July 2002. The researchers searched the terms: bilberry, *V. myrtillus*, *Myrtili folium*, anthocyanosides, and vision (Canter & Ernst, 2004). Web sites promoting herbal medicines were also 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. Two independent reviewers extracted all data from all English articles, and articles in other languages were checked by associates who were native or

fluent speakers. Only placebo-controlled studies investigating bilberry were included in the systematic review. Doses ranged from 12 to 2,880 mg of anthocyanosides daily for up to 28 days. Of the 2,295 participants, 94 complained of side effects that were mainly gastrointestinal or related to the skin or nervous system. No toxic effects were reported in any of the studies. The authors found that the most rigorous clinical studies do not support the hypothesis that *V.myrtillus* anthocyanosides improve night vision in healthy subjects. Out of the 12 trials meeting the inclusion criteria for this systematic review, 5 were randomized controlled trials, and 4 of these found no significant effects of *V.myrtillus*-extracted anthocyanosides on vision in reduced-light conditions. One randomized controlled trial and seven lesser-quality placebo-controlled trials all reported positive effects on at least one outcome measure related to vision in reduced light. The authors noted that the obvious association among methodological rigor, recent publication, and negative outcome is confounded, however, by several factors, including dose, possible geographical variations in extract composition, and choice of subjects. It should also be noted that methods used to obtain and interpret electroretinograms in the older trials differ from the standardized procedures now used. Limitations of this study include the possibility of positive outcome bias due to the use of published sources to find articles.

- A double-blind, placebo-controlled, crossover study examined the effects of high-dose bilberry extract over a 3-week period (Muth et al., 2000). Bilberry extract at a dose of 160 mg or placebo was given three times daily to 15 subjects. At the end of 21 days, patients were crossed over to the other treatment arm. Results failed to demonstrate any effect on night visual acuity or night contrast sensitivity. Subjects were healthy young males. The authors reported that two had "below-average" night vision parameters, and "subset analysis" did not show any improvement in these two. This small study with no power calculation does not allow for definitive conclusions.
- Levy and Glovinsky (1998) performed a double-blind, placebo-controlled, crossover study to examine the effect of a single oral dose of bilberry extract (VMA) on night vision in normal individuals. The researchers evaluated three parameters of night vision (scotopic retinal threshold (SRT), dark adaptation rate (DAR), and mesopic contrast sensitivity (MCS)). Sixteen normal volunteers were tested, and no significant effect was noted. The study was more carefully controlled than the studies from the 1960s; patients were normal individuals with no report of visual impairments. The study population was small. With a sample size of 16 and no power calculation conducted, a positive result

could have been missed. It is also possible that the duration of therapy was insufficient and that more than one dose of VMA is needed in order to elicit an improvement in night vision.

- In the late 1990s, Israeli investigators reported similar negative results in a trial using bilberry (Zadok et al., 1997, 1999). This double-blind, placebo-controlled, crossover study in 18 subjects used a lower dose of bilberry (12–24 mg anthocyanosides) given twice daily for 4 weeks. No statistically significant improvements in night vision were observed, as measured by full-field absolute SRT, DAR, or MCS. Although this trial was small, a power calculation found the sample to be adequate to measure the stated outcomes. Nonetheless, with a sample size of 18, the adequacy of the sample size must come into question. The power was calculated to 80%, which is a standard approach, although this leaves a 20% chance that there are true benefits of therapy.
- Jayle and Aubert (1964) conducted an early randomized crossover trial in 40 healthy subjects. Individuals received anthocyanosides from bilberry and were found to have a statistically significant small improvement in night vision. However, details of blinding, randomization, and the measurement instrument were limited, thus reducing the clinical applicability of these results. A follow-up randomized placebo-controlled trial by the same author administered 1,000 mg of anthocyanosides from bilberry to 60 healthy individuals (Jayle et al., 1965). Again, a moderate statistically significant improvement was documented, although blinding and randomization were not adequately reported.

## *PRODUCTS STUDIED*

### *Brands Used in Human Studies*

- Tegens® (Europe).
- Mirtogenol®, a trademark of Indena S.p.A. and Horphag Research Ltd., is a patent pending proprietary combination of standardized bilberry extract Mirtoselect® and French maritime pine bark extract Pycnogenol®.

### *Brands Shown to Contain Claimed Ingredients Through Third-Party Testing*

- *Consumer Lab*: Nutrilite® Bilberry with Lutein, Sundown® Lutein, Vitamin World® Naturally Inspired™HerbaVision™Lutein. Last accessed 7/25/08.

- *Consumer Reports*: NA. Last accessed 7/25/08.
- *Natural Products Association*: lbi Imports, Ltd. Bilberry, Enzymatic Therapy Bilberry Extract, Flora, Inc. Flora Vision, Gaia Herbs Bilberry Leaf & Berry, GNC Fingerprinted Bilberry, Great American Health Doctor's A-Z Bilberry, Indiana Botanic Gardens Bilberry, JR Carlson Labs Bilberry + Vitamin A and E, MegaCare Inc. Eye Food, Natrol Bilberry, Nature's Herbs Power-Herbs Bilberry-Power, Nature's Life Bilberry i-sight, Nature's Plus Herbal Actives Bilberry, Nature's Plus Liquid Bilberry, Nature's Plus H.A. Bilberry, Nature's Way Standardized Bilberry Extract, Optimal Nutrients Bilberry, Optio Health Products, Inc. Bilberry Extract, Solgar Bilberry, Threshold Enterprises Source Naturals—Bilberry Extract 100 mg, Tree of Life Bilberry. Last accessed 7/25/08.
- *NSF International*: Report on *Anthocyanin Content in Bilberry by pH-Differential Spectrophotometry.* Last accessed 7/25/08.
- *U.S. Pharmacopeia*: NA. Last accessed 7/25/08.

### *U.S. Equivalents of Most Commonly Recommended European Bbrands*

Not applicable.

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